PB91-225680

Drinking Water Criteria Document for Uranium

(U.S.) Environmental Protection Agency, Washington, DC

Jun 91

U.S. Department of Commerce
National Technical Information Service
NTIS

PB91-225680

DRAFT

DRINKING WATER CRITERIA DOCUMENT
FOR
URANIUM

Updated and revised by

Clement International Corporation
1201 Gaines Street
Ruston, Louisiana 71270

and

Wade Miller Associates
1911 North Myer Drive
Arlington, Virginia 22209

June 1991

Prepared for

Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC 20460

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before complet

1. REPORT NO.	2.	3. PB91-225680

4. TITLE AND SUBTITLE Drinking Water Criteria Document for Uranium	5. REPORT DATE 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Clement International Co. and Wade Miller Assoc.	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Drinking Water Standards Division: OGWDW: EPA WH550D : 401 M St. , SW Washington, DC 20460	10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Drinking Water Standards Division: OGWDW: EPA WH550D 401 M St. , SW Washington, DC 20460	13. TYPE OF REPORT AND PERIOD COVERED Health Criteria Document 14. SPONSORING AGENCY CODE OGWDW

15. SUPPLEMENTARY NOTES

Review Draft

16. ABSTRACT

This document provides the health effects basis to be considered in establishing the MCLG for uranium. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and the mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in this document. The comprehensive literature search in support of the analysis of health effects, exposure and occurrence in this document includes information published up to January, 1991; however, more recent information may have been added during the review process.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
health criteria document pharmacokinetics dose-response mechanisms of toxicity	MCLG	

18. DISTRIBUTION STATEMENT unlimited	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES [redacted]
	20. SECURITY CLASS *(This page)*	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1991; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

James R. Elder
Director
Office of Ground Water and Drinking Water

TABLE OF CONTENTS

Page

FOREWORD i

LIST OF TABLES iv

LIST OF FIGURES vii

I. SUMMARY I-1

II. PHYSICAL AND CHEMICAL PROPERTIES II-1

- A. General Properties II-1
- B. Source, Production, and Use II-4
- C. Environmental Fate and Stability II-8
- D. National Occurrence and Exposure from Public Water Supplies II-10
  - 1. Introduction II-10
  - 2. General Information II-11
  - 3. Sources of Drinking Water Occurrence Information II-13
  - 4. Methodology and Assumptions II-16
  - 5. National Occurrence Estimates II-20

III. HUMAN EXPOSURE III-1

- A. Drinking Water III-1
- B. Diet III-1
- C. Ambient Air III-14
- D. Total Exposure and Relative Source Contribution III-14
  - 1. Analytical Approach III-15
  - 2. Results III-16

IV. TOXICOKINETICS IV-1

- A. Absorption IV-1
  - 1. Humans IV-4
  - 2. Animals IV-9
- B. Distribution IV-13
  - 1. Blood IV-13
  - 2. Kidney and Other Soft Tissues IV-14
  - 3. Distribution Within the Kidney and Elimination from the Kidney IV-15
  - 4. Distribution to Bone and Teeth IV-16
  - 5. Distribution Within the Bone IV-18
  - 6. Elimination from Bone IV-19
- C. Excretion IV-19
  - 1. Human IV-19
  - 2. Animal IV-21
- D. Bioaccumulation and Retention IV-21

TABLE OF CONTENTS (continued)

Page

V. HEALTH EFFECTS IN ANIMALS V-1

- A. Short-term Exposure V-1
  - 1. Oral Studies V-1
  - 2. Inhalation Studies V-4
  - 3. Intravenous Studies V-4
  - 4. Subcutaneous Studies V-6
- B. Long-term Exposure V-8
- C. Reproductive/Developmental V-11
- D. Mutagenicity V-14
- E. Carcinogenicity V-14
- F. Summary V-15

VI. HEALTH EFFECTS IN HUMANS VI-1

- A. Clinical Case Studies VI-1
- B. Epidemiological Studies VI-1
- C. High Risk Populations VI-3
- D. Summary VI-4

VII. MECHANISM OF TOXICITY VII-1

- A. Ionizing Energy Deposition VII-1
- B. Radionuclide Dosimetry VII-2

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS VIII-1

- A. Noncarcinogenic Effects VIII-1
  - Method for Quantification of Noncarcinogenic Effects VIII-1
  - Quantification of Noncarcinogenic Effects VIII-4
  - 1. One-day and Ten-day Health Advisory VIII-4
  - 2. Longer-Term Health Advisory VIII-6
  - 3. Reference Dose and Drinking Water Equivalent Level . . . VIII-7
- B. Carcinogenic Effects VIII-8
  - Method for Quantification of Carcinogenic Effects VIII-8
  - Quantification of Carcinogenic Effects VIII-10

IX. UNCERTAINTY ANALYSIS IX-1

- A. Uncertainty in Choice of Metabolic Model IX-1
- B. Uncertainty in Distribution of Isotope IX-3
- C. Uncertainty in Dosimetric Calculations IX-3
- D. Uncertainty in Specific Organ Risks IX-5
- E. Uncertainty in Other Factors Influencing Risk IX-6
- F. Conclusion IX-7

X. REFERENCES X-1

LIST OF TABLES

Table No.		Page
II-1	Percent Occurrence and Radioactive Properties of Naturally Occurring Isotopes of Uranium	II-2
II-2	Physical and Chemical Properties of Uranium and Some Uranium Salts	II-5
II-3	Summary of Uranium Occurrence in the National Inorganics and Radionuclides Survey	II-15
II-4	Summary Statistics from the Log Regression Analysis for Uranium	II-18
II-5	Estimated Cumulative National Occurrence of Uranium in Community Ground Water Supplies: By Total Uranium Concentration	II-21
II-6	Estimated Cumulative Occurrence of Uranium in Non-transient Non-Community Ground Water Supplies: By Total Uranium Concentration	II-22
II-7	Estimated Cumulative National Occurrence of Uranium in Community Surface Water Supplies: By Uranium Activity	II-23
II-8	Estimated Cumulative Occurrence of Uranium in Nontransient, Non-Community Surface Water Supplies: by Uranium Activity	II-24
II-9	Estimated Cumulative National Occurrence of Uranium in Community Surface Water Supplies: By Total Uranium Concentration	II-25
II-10	Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Total Uranium Concentration	II-26
II-11	Estimated Cumulative National Occurrence of Uranium in Community Surface Water Supplies: By Uranium Activity	II-27
II-12	Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Uranium Activity	II-28
III-1	Estimated Cumulative Population (in thousands) Exposed to Uranium from Community Ground Water Supplies: By Total Uranium Concentration	III-2
III-2	Estimated Cumulative Population (in thousands) Exposed to Uranium from Non-Transient, Non-Community Ground Water Supplies: By Total Uranium Concentration	III-3

LIST OF TABLES (continued)

Table No. Page

III-3 Estimated Cumulative Population (in thousands) Exposed to Uranium from Community Surface Water Supplies: By Total Uranium Concentration III-4

III-4 Estimated Cumulative Population (in thousands) Exposed to Uranium from Non-Transient, Non-Community Surface Water Supplies: By Total Uranium Concentration III-5

III-5 Estimated Cumulative Population (in thousands) of Uranium in Community Ground Water Supplies: By Uranium Activity III-6

III-6 Estimated Cumulative Population (in thousands) of Uranium in Non-Transient, Non-Community Ground Water Supplies: By Uranium Activity III-7

III-7 Estimated Cumulative Population (in thousands) of Uranium in Community Surface Water Supplies: By Uranium Activity III-8

III-8 Estimated Cumulative Population (in thousands) of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Uranium Activity III-9

III-9 Uranium Dietary Intake Studies III-11

III-10 Modeled Dietary Intake of Uranium III-13

III-11 Summary Statistics for the Total Exposure Distribution for Uranium III-18

III-12 Summary Statistics for the Percent From Drinking Water Distribution for Uranium III-21

IV-1 Calculation of Oral Absorption Fractions in Humans for Uranium . IV-2

IV-2 Calculation of Oral Absorption Fractions in Animals for Uranium . IV-3

VIII-1 A Comparison of 30-Day, 1-Year, and 2-Year NOAELs/LOAELs for Uranium Toxicity Used for the Development of the Ten-day and Longer-term HAs VIII-5

VIII-2 50-Year Committed Absorbed Dose per Unit Intake from Uranium in Drinking Water VIII-12

VIII-3 Organ-Specific Lifetime Cancer Risks Used in the RADRISK Model from High-LET and Low-LET Irradiation VIII-13

VIII-4 Estimated Risk of Death from Leukemia or All Causes from Ingestion of 70.765 pCi Uranium VIII-15

LIST OF TABLES (continued)

Table No. Page

VIII-5 Adjusted Risk of Death from Leukemia from Ingestion of 70.765 pCi Uranium VIII-16

VIII-6 Adjusted Urinary Cancer Risks VIII-18

VIII-7 Estimated Lifetime Risk for Ingestion of 1 μCi of Uranium in Drinking Water VIII-19

VIII-8 Water Concentration of Uranium in Drinking Water to Yield a Specific Risk for Lifetime Consumption VIII-19

IX-1 Comparison of Burden Predicted in Bone and Kidney by ICRP and by Wrenn et al. IX-3

LIST OF FIGURES

Figure No. Page

II-1 Principal Decay Scheme for the Uranium Series II-3

III-1 Distribution of Total Uranium Exposure from Simulation Model . III-17

III-2 Distribution of Drinking Water Contribution to Total Intake from Simulation Model III-20

I. SUMMARY

Uranium is a naturally occurring element which makes up about 2 ppm of the earth's crust. It is found in rocks and ores throughout the earth, with greatest concentrations in the United States being in the western states. It is naturally found in minerals such as carnotite and pitchblende and in rocks such as phosphate and lignite. It is naturally found in both freshwater and seawater in concentrations of about 0.002 ppm.

Uranium is naturally released into the air and water through the weathering of rocks. Anthropogenic releases into the atmosphere include open pit and underground mining and milling and manufacturing processes. Uranium is also released during the production of phosphate fertilizers and the improper disposal of uranium-containing waste.

Uranium is a radioactive element with three major isotopes. The principal isotopes of concern in drinking water are uranium-234 and uranium-238. For nuclear fuel, uranium is enriched to uranium-235. About 99 percent of natural uranium is in the form of uranium-238, which has a long half-life of about 4.5 billion years. Uranium-234 has a shorter half-life of 0.2 million years. Uranium eventually decays via beta and alpha emissions to thorium, radium, and radon, and finally to stable lead.

The major uses of enriched uranium are for nuclear power generation and for military weapons. Depleted uranium is also largely used for military ammunition.

Uranium can exist in various oxidative states, but uranium^{+6} and uranium^{+4} are the most common and often form compounds with other elements. Compounds that are soluble in water include uranium tetrachloride, uranyl nitrate hexahydrate, and uranyl fluoride. Important compounds which are far less water soluble include uranium dioxide and uranium tetrafluoride.

Uranium has been detected in 72 percent of the 990 ground water sites sampled by the National Inorganics and Radionuclides Survey (NIRS) conducted by the EPA's Office of Drinking Water during 1984-1986. The median, mean and maximum values were 0.525, 2.55 and 88.2 µg/L, respectively. These NIRS data are also presented in picocurie (pCi) units, using the conversion factor of 1.3 pCi per µg uranium. An estimated 52 million people in the United States are exposed to uranium levels above 0.10 pCi/L from ground water supplies of drinking water and an estimated 115 million people are exposed to this level from surface water supplies.

The total personal intake of uranium is about 2 pCi/day. About half of the total intake is from drinking water; the remainder is from foods. Very little intake is from the air.

Once uranium is swallowed, it is poorly absorbed from the gastrointestinal tract. Various studies in humans and animals indicate that the absorption factor probably lies somewhere between 0.05 percent and 22 percent of the amount ingested. These data are obtained from laboratory experiments in animals and humans, as well as from estimates of chronic intake and measurements of output from humans. A reasonable and conservative estimate of the amount absorbed by the gastrointestinal tract in humans for acute or chronic periods is 5 percent ($f_1 = 0.05$).

Uranium is quickly distributed to several organs of the body, principally to the kidneys and bone. Within the kidney, uranium is concentrated in the proximal renal tubules. Here it has a biphasic half-life, with the first elimination occurring within several days, and the later within several months. In bone, uranium is concentrated on surfaces in close proximity to the vascular supply. Uranium which is consumed in drinking water is largely excreted unabsorbed in the feces. The remaining fraction which was absorbed into the bloodstream is excreted in the urine. A toxicokinetic model for uranium uptake and retention has been developed by the International Council on Radiation Protection (ICRP) and is used by the EPA. The uranium model assumes that the absorption from the gastrointestinal tract is a factor of 0.05, and that the fractional uptake in tissues is 0.22 to bone, 0.12 to kidneys, 0.12 to other tissues, and 0.54 excreted.

Due to its properties as a heavy metal and a radioisotope, uranium has the potential to exert two different types of toxic effects in humans and animals: chemical effects caused by the metal itself, and effects caused by the radiation. The main concern for the chemical effects of uranium is its toxic effects on the kidney. The main concern for the radiation effects is the potential to cause cancer.

Both animal and human studies are available which indicate that the kidney is the target organ for uranium toxicity following both short- and long-term exposures. Uranium damages the proximal convoluted tubules in the kidney, as evidenced by both biochemical and anatomical studies. Animal studies also show that reproductive parameters and fetal development are affected in animals exposed to uranium by the oral route.

There are no studies which examine the carcinogenicity of uranium administered via the oral route. However, since uranium is a radioactive element, it is expected that cancer is also a cause for concern following exposure by the oral route. Uranium miners and millers have shown increases in lung cancer and lymphomas which have been attributed to the inhalation of uranium particles.

Quantitative risk estimates for the noncancer (kidney) effects and cancer have been performed. The quantitative risk estimates indicate that the potential for noncancer kidney effects is probably greater than the risk for cancer. Therefore, the Health Advisories (HA) and Reference Dose (RfD) have been derived for adverse kidney effects.

The Health Advisories for uranium have all been derived from a 30-day study in rabbits, which have been shown to be the most sensitive species for development of adverse kidney effects. Rabbits fed doses of 2.8 mg uranium/kg/day as uranyl nitrate showed moderate renal damage, and these effects were more severe at higher dose levels. Using 2.8 mg/kg/day as a Lowest-Observed-Adverse-Effect-Level (LOAEL), a ten-day health advisory of 30 µg uranium/L was calculated for a 10 kg child. This incorporates an uncertainty factor of 1000 to account for the use of a LOAEL from an animal study, in accordance with National Academy of Science/Office of Drinking Water guidelines. This value is also used for the one-day and the long-term HA for a child. The long-term HA for a 70 kg adult is based on the same study and is calculated as 0.1 mg/L. The RfD and Drinking Water Equivalent Level (DWEL) are calculated from the same study and are 3 µg uranium/kg/day, and 0.1 mg/L, respectively.

The risks for the development of cancer from uranium exposure have been calculated using the RADRISK model. The estimated lifetime risk for ingestion of 1 µCi of uranium-234 or uranium-238 in drinking water is 1.6×10^{-5}. A concentration of 120 pCi (92 µg)/L of uranium-234 and uranium-238 in drinking water yields a risk of 1×10^{-4} for the incidence of cancer for a lifetime of consumption and a concentration of 170 pCi (130 µg/L) yields a risk of 1×10^{-4} for death from cancer for a lifetime of consumption.

II. PHYSICAL AND CHEMICAL PROPERTIES

A. GENERAL PROPERTIES

Uranium, an actinide element, is the heaviest, naturally occurring element. All of its natural isotopes are radioactive. Essentially all of the naturally occurring uranium consists of the isotopes uranium-238, uranium-235, and uranium-234, since only these isotopes have half-lives of appreciable length on a geological scale. Uranium-230 contributes a minor amount of the total uranium activity. The percent occurrence and radioactive properties of naturally occurring isotopes of uranium are presented in Table II-1 (Lide 1990). The principal decay scheme of the uranium (uranium-238) series shown in Figure II-1 includes the common synonyms of the decay products, the half-lives of each isotope, and the energy of the principal alpha particle emitted (NCRP 1984).

In natural uranium, the radioactivity from uranium-238 accounts for approximately half the radioactivity, and radiation from uranium-234 and uranium-235 accounts for the other half. During the enrichment process employed in creating fuel for nuclear reactors, the uranium-235 level (0.72 percent by weight) is increased up to 2 to 3 percent by weight (Weigel 1983).

Uranium exists in four oxidative states (+3 through +6). The hexavalent state (+6) is the most stable. Uranium^{+3} is comparatively unstable; it is readily oxidized in air to the +4 state and more slowly oxidized in water. Uranium^{+4} is reasonably stable and forms hydroxides, hydrated fluorides, and phosphates of low solubility; it also oxidizes slowly in the air. The uranium^{+5} state is more stable in an acidic (pH 2 to 6) solution. The most common hexavalent state occurs as hexafluoride (UF_6). Uranium also forms oxohalides (UOF_5 and $UOCl_5$). The only common uranium salts are the uranyls, the most important of which is the uranyl nitrate $UO_2(NO_3)_2$ (Weigel 1983).

Uranium may exist in one of three allotropic forms: orthorhombic, tetragonal, or body-centered cubic. It is a chemically reactive metal that combines directly with most elements. Its reaction with water is complex; boiling water forms UO_2 and hydrogen, the latter reacting with the metal to form a hydride, which disintegrates. Metal ions in an aqueous solution can

Table II-1. Percent Occurrence and Radioactive Properties of Naturally Occurring Isotopes of Uranium

Isotope	Percent (by weight) in natural uranium	Alpha energies, MeV (abundance of alpha emission)	Half-life (years)
Uranium-234	0.0055	4.78 (72.5%) 4.72 (27.5%)	2.45×10^5
Uranium-235	0.72	4.60 (5%) 4.40 (55%) 4.37 (6%) 4.36 (11%) 4.22 (5.7%) Others (13.5%)	7.04×10^8
Uranium-238	99.27	4.20 (77%) 4.15 (23%)	4.46×10^9

SOURCE: Adapted from Lide (1990).

Figure II-1. Principal decay scheme for the uranium series (y = years; d = days; m = minutes; s = seconds).

To be provided by Wade Miller and Associates

SOURCE: NCRP (1984).

form very complex species. In addition to the four oxidative states, complexing reactions occur under appropriate conditions with all ions other than ClO_4. Hydrolytic reactions also occur, leading to polymeric ions. Other complex ions are formed with citrate and other organic acids (Weigel 1983).

Spontaneous ignition of finely crushed uranium may occur at room temperature in the presence of air, oxygen, and water. At temperatures of 200 to 400°C, uranium powder may ignite in atmospheres of CO_2 and N_2. The oxidation of uranium under certain conditions may generate sufficient energy to cause an explosion (Gindler 1973). Interactions also yield known species of phosphates, $UO_2H_2PO_4^{+}$ and $UO_2H_3PO_4^{++}$. At pH 6 and below, uranium forms very stable complexes with oxygen-rich humic and fulvic acids under natural environmental conditions. Uranium interacts with peats, coals, asphalts, shales, phosphorites, and carbonates (Katz and Rabinowitch 1951).

The physical and chemical properties of uranium and some uranium salts are presented in Table II-2.

B. SOURCE, PRODUCTION, AND USE

Uranium is widely distributed in nature and accounts for approximately 2 ppm of the earth's crust (Weigel 1983). It is present in a variety of minerals such as carnotite, pitchblende, uranite, autunite, uranophane, davidite, and torbernite. It is also found in phosphate rock, lignite, and monazite sands (Weast 1986). Uranium is also encountered in seawater at concentrations of approximately 0.001 to 0.003 ppm (Kathren 1984). Most economically attractive uranium ores have uranium concentrations in excess of 1,000 ppm (Stokinger 1981, Weigel 1983). The major natural sources of uranium are hydrothermal veins in Saxony, Zaire, and Canada; sedimentary rocks in Colorado, Arizona, Wyoming, Texas, Utah, and New Mexico; and pyritic conglomerate beds of pre-Cambrian age in Witwatersrand and Ontario (ILO 1983, EPA 1985). Currently, open-pit mining, in situ leaching, and underground mining are three techniques for the mining of uranium-containing ores (EPA 1985).

Table II-2. Physical and Chemical Properties of Uranium and Some Uranium Salts

Chemical	Formula	% Uranium	Physical state	Density	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility
Uranium	U	^{234}U(0.006%) ^{235}U(0.7%) ^{238}U(99%)	Dense, silvery solid	19.0	238.03	1132	3818	Is attacked by water in in finely powdered state, acids, and peroxides but is inert toward alkalies
Uranium and dilute dioxide	UO_2	88.15	Black crystals	10.97	270.07	2865	--*	Insoluble in water acids; soluble in concentrated acids
Uranium hexafluoride	UF_6	67.62	Colorless, volatile crystals	5.06	352.07	64.8	--	Reacts vigorously with water, alcohol, ether and most metals; soluble in liquid chlorine, bromine, and carbon tetrachloride, chloroform, nitrobenzene, sym-tetrachloroethane
Uranium tetrachloride	UCl_4	62.67	Dark green, octahedral crystals	4.72	379.90	590	791	Freely soluble in water and polar organic solvents
Uranium tetrafluoride	UF_4	75.80	Green crystals	6.70	314.07	1036	--	Insoluble in water; soluble in concentrated acids and alkalies
Uranium trioxide	UO_3	83.22	Red or brownish yellow powder	7.29	286.07	--	--	Insoluble in water; soluble in acids
Uranium peroxide dihydrate	$UO_4 \cdot 2H_2O$	78.81	Pale yellow crystals	--	338.03	--	--	Decomposes to UO_3 and O_2 on contact with water and to uranyl salts and O_2 on contact with acids
Uranyl chloride	UO_2Cl_2	69.82	Bright yellow crystals	5.43	340.98	578	900	Freely soluble in water; soluble in polar organic solvents
Uranyl nitrate hexahydrate	$UO_2(NO_3)_2 \cdot 6H_2O$	60.41	Yellow, rhombic crystals	2.807	502.13	60.2	118	Soluble in water, alcohol, and ether

Table II-2. Continued

Chemical	Formula	% Uranium	Physical state	Density	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility
Uranyl[b] fluoride	UO_2F_2	76.8	Pale yellow, rhombohedral hygroscopic	6.37	308.00	Decomposes at 300°	--	Very soluble in water
Sodium diuranate	$Na_2U_2O_7$	75.08	Yellow-orange solid	--	634.04	--	--	Insoluble in water; soluble in dilute acids
Triuranium octoxide	U_3O_8	--	Olive-green to black solid	8.39	842.09	Decomp ses at 1300° to UO_2	--	Insoluble in water; soluble in HNO_3, H_2SO_4

[a] No information was found.
[b] SOURCE: HSDB 1991

SOURCE: Budavari (1989); Sax and Lewis (1987).

While the total activity of uranium-238 and uranium-234 is in equilibrium on a global scale, uranium-238 and uranium-234 generally are not in equilibrium within specific samples (particularly rocks and soil). This is believed to be due to displacement of uranium-234 from the crystal lattice by recoil at the time of disintegration of uranium-234. The displaced uranium-234 is capable of being oxidized to the hexavalent form and is thus more easily leached into the surrounding water than the parent uranium-238 (NAS 1983).

Uranium is released to the environment by both man-made and natural sources. Man-made sources include the following: mining, milling, handling, and processing of uranium ores or their endproducts; production of phosphate fertilizers from phosphate rocks containing higher levels of uranium than natural soils; and improper disposal of uranium-containing waste (Cottrell et al. 1981, Hart et al. 1986, Swanson 1985, Stelling 1980, Yang and Edwards 1984, NCRP 1984). Natural sources include volcanic eruptions that increase the uranium concentrations in air and rainwater and rocks and soil (Kuroda et al. 1984).

Uranium production increased from 1975 to 1980, but declined sharply thereafter. The number of domestic mines for uranium production decreased from a peak of 432 in 1979 to 135 in 1983 and to only 40 in 1984 (EPA 1985). As of August 1986, the conventional uranium milling industry in the United States consisted of five active mills, 11 mills on a stand-by status and 10 that were either decommissioned or were in the process of being decommissioned (EPA 1986). It has been forecasted that the total domestic production of triuranium octaoxide will decrease from 10,000 tons in 1984 to 7,600 tons in 1990 (EPA 1985).

Uranium is used primarily in the commercial nuclear power industry and in weapon systems (Stokinger 1981). Depleted uranium (natural uranium depleted of uranium-235) is used to manufacture armor-piercing ammunition for the military, in inertia guidance devices and gyro compasses, as a counterweight for missile reentry vehicles, as radiation shielding material, and as x-ray targets (USDI 1980). According to USDI (1980), the major uses of depleted uranium in the United States in 1978 were as follows: military ammunition, 71.8 percent; counterweight, 11.4 percent; radiation shielding, 13.6 percent; and chemical catalyst, 3.2 percent. Uranium dioxide is used to extend the lives of large incandescent lamps used for photography and motion pictures. Uranium compounds are used in photography for toning, in leather and wood industries for stains and dyes, and in silk and wool industries as mordants. Ammonium diuranate is used to produce colored glazes in ceramics. Uranium carbide is a good catalyst for the production of synthetic ammonia (Hawley 1981). For many years, uranium was used in dental porcelains, but this practice has been discontinued (Thompson 1976).

C. ENVIRONMENTAL FATE AND STABILITY

The four most important factors controlling the transport and mobility of uranium in natural waters are: oxidation-reduction potential (E_h) of the water, pH, characteristics of complexing agents or ligands, and the nature of sorbing materials in water. The E_h of water is important in controlling the mobility of uranium in water in that the uranium in the +6 oxidation state is highly soluble, thus accounting for its wide distribution in seawater, freshwater, and hydrothermal deposits (Kirk-Othmer 1978). Concentrations of uranium in freshwater range from 0.02 to 200 µg/L (NAS 1977). Studies of the isotopic composition of uranium in natural waters indicate that the activity of uranium-234 exceeds that of uranium-238 (Hess et al. 1985). The ratio may be as high as 8:1 but averages between 1:1 and 3:1 (EPA 1985). In anoxic waters where the E_h values are such that uranium^{+6} is reduced to uranium^{+4}, the concentration of soluble uranium will decrease because of the inability of uranium^{+4} to form soluble complexes as readily as uranium^{+6} (Allard et al. 1979, Herczeg et al. 1988). The stability of these complexes will depend on the pH of the water. Uranium is likely to be in solution as carbonate complex in oxygenated water with high alkalinity (Herczeg et al. 1988), but in water with pH less than 6 and containing low concentrations of inorganic ion and high concentrations of dissolved organic matter, uranium will be in solution as soluble organic complexes (Brunskill and Wilkinson 1987). Inorganic ions or organic ligands that can form soluble complexes with uranium will increase its mobility in water. In most waters, sediments will be a sink for uranium and the concentration of uranium in sediments and suspended solids will be several orders of magnitude higher than its concentration in water (Brunskill and Wilkinson 1987, Swanson 1985). Sediments and suspended solids in water with higher uranium sorption characteristics will reduce the mobility of uranium in solution. The sorption of uranium may be due to physicochemical interaction (e.g., ion-exchange) or physical adsorption. Both of these processes may be pH-dependent. For example, in oxic water with high alkalinity, anionic carbonate complexes may readily exhibit ion-exchange interactions with hydrated iron oxides present in sediments. At lower pH levels and higher temperatures, the carbonate complex may dissociate, forming cationic uranyl salts; silica may be a better sorbent than iron oxide (Ames et al. 1982). Uranium may be removed from solution by physical adsorption isotherm (Ames et al. 1982).

As in water, the factors controlling the mobility of uranium in soil include the oxidation-reduction potential (E_h), pH, and the sorbing characteristics of the sediments and soils. Similarly, the significant reactions of uranium in soil are formation of complexation with anions and ligands (e.g., CO_3^{-2}, OH^{-1}, humic acid) and reduction of uranium^{+6} to uranium^{+4}. These reactions are important in controlling the mobility of uranium in water and soil. Other factors that control the mobility of uranium in water and soil are E_h, pH, and the sorbing characteristics of the sediments and soils. Uranium is strongly adsorbed and retained by the soil when present in the +4 oxidation state and may be bound with organic matter and clay colloids; uranium concentrations of 100 ppm in water were almost completely adsorbed on several of the soils studied by Brown (1983). Conditions that increase the rate of formation of soluble complexes and decrease the rate of sorption of labile uranium in soil and sediment are expected to enhance the mobility of uranium (Allard et al. 1979, 1982; Ames et al. 1982, Brunskill and Wilkinson 1987, Herczeg et al. 1988, Premuzic et al. 1985).

Plant uptake of uranium from soils that are naturally high in this element provided the only data available on plant accumulation. Because high concentrations of uranium in plants are not phytotoxic, plants containing large amounts of uranium may provide a food-chain link to animals. Plant uptake of uranium is usually low because uranium is so strongly fixed in surface soils (Brown 1983). In addition, uranium uptake in plants may be restricted to the root system where it is transported from soil to the outer root membrane and not to the interior of the root (Sheppard et al. 1983). No significant translocation of uranium from soil to the above ground parts of plants has been observed (Van Netten and Morley 1983). Because of adsorption by roots, consumption of potatoes, radishes, and other root vegetables grown in high uranium-containing soils may be a significant source of exposure (Van Netten and Morley 1983). The use of phosphate fertilizers is known to elevate the concentration of uranium in food to levels of approximately 8 ng/g (Reid et al. 1977). In a review by Garten (1978), the soil-to-plant concentration ratio of uranium was estimated to range from $3x10^{-5}$ to $9x10^{-2}$. The NCRP (1984) recommends a default value between $3x10^{-4}$ and $3x10^{-3}$ (wet vegetation to dry soil).

D. OCCURRENCE OF URANIUM IN PUBLIC WATER SUPPLIES

1. Introduction

The EPA Office of Drinking Water (ODW) is currently developing national primary drinking water regulations for naturally occurring and man-made radionuclides including uranium, the subject of the occurrence and exposure assessment presented in this report.

Occurrence and exposure assessments support several aspects of the drinking water regulatory development process. Information on the distribution of contaminant occurrence levels in public water supplies of various source and size characteristics provides ODW with a basis for estimating the number of systems and the size of the affected populations currently experiencing contaminant levels exceeding the Maximum Contaminant Level (MCL) alternatives under consideration. That information is critical for conducting the cost impact analyses of the regulatory alternatives. The information on contaminant occurrence levels also supports the identification of the Best Available Technology (BAT) necessary for setting MCLs and for granting variances. The exposure information, particularly the analysis of the contribution of drinking water to total intake relative to other sources of exposure, is important for setting the Maximum Contaminant Level Goal (MCLG) for a contaminant. In addition, the exposure information provides the basis for the "baseline" health impacts assessment of current contaminant levels and for evaluating the health benefits of the regulatory alternatives.

Two previous versions of a drinking water occurrence and exposure assessment document addressing uranium have been prepared in support of EPA's analysis of regulatory options (SAIC 1987; WMA 1990). Both of those earlier documents presented the uranium occurrence and exposure information primarily in terms of activity levels, expressed in pCi units, reflecting the concern for the carcinogenic effects associated with alpha particle emissions from the radioactive decay of the three uranium isotopes. However, exposure to uranium is also of concern because of its chemical toxicity, which is related to the total mass of uranium rather than to specific amounts of each isotope present.

EPA is currently considering both the option of setting the uranium MCL in units of µg/L on the basis of its chemical toxicity, as well as the option of setting the MCL in units of pCi/L based on its carcinogenicity. The primary purpose for this revision to the previous uranium occurrence documents is to present the occurrence and exposure assessment in units of mass as well as in units of activity.

This chapter presents quantitative estimates of the number of community and non-transient non-community ground water supplies and surface water supplies of various sizes expected to have uranium present in excess of certain levels of interest for evaluating regulatory alternatives. Since uranium is a public health concern both because of its chemical toxicity and its radioactivity, the uranium occurrence estimates are provided both in terms of systems expected to exceed certain uranium concentrations (µg/L) and system expected to exceed certain activity levels (pCi/L). The data sources, methodology, and assumptions employed in arriving at these national estimates are also discussed.

2. General Information

There are three naturally occurring isotopes of uranium: uranium-238, uranium-235, and uranium-234. Natural uranium is widely distributed in rocks and minerals in the earth's crust, and it occurs in both surface water and ground water. The relative abundance of the three natural uranium isotopes in crustal materials is about 99.283 percent uranium-238 by weight, 0.711 percent uranium-235 and 0.0054 percent uranium-234 (NAS 1988). However, the relative abundance of the three isotopes in water can vary somewhat from these values, although even in those cases uranium-238 remains by far the predominant isotope present by weight.

Uranium-238 is the first member of the uranium-238 decay series; uranium-234 is one of the daughter products formed within that series. Uranium-235 is the first member of the uranium-235 decay series (also known as the actinium decay series). All three uranium isotopes undergo radioactive decay by alpha particle emission. The half-lives of the three isotopes are:

Uranium-238: 4.5×10^9 years
Uranium-235: 7.1×10^6 years
Uranium-234: 2.5×10^5 years

Although the half-lives of all three isotopes are relatively long, the fact that the half-life of uranium-234 and uranium-235 are three to four orders of magnitude less than that of uranium-238 is significant with regard to the overall activity level of uranium in an environmental sample. Since the activity of a given mass of uranium (i.e., the number of alpha emissions per unit time) depends upon the amount of each isotope present, the greater the relative abundance of the more rapidly decaying uranium-234 and uranium-235, the higher the activity will be. The significance of this with respect to uranium in drinking water is discussed further below.

Uranium in water can occur both in dissolved forms and attached to suspended particles (ORNL 1981). The predominant species of uranium present in water involve the uranyl ion, UO_2^{2+}, which forms stable complexes with phosphate and carbonate. According to Sorg (1990), soluble carbonate complexes of UO_2^{2+} are the predominant anion species present in natural waters of pH 7 to 10, particularly $UO_2(CO_3)_2^{2-}$, and $UO_2(CO_3)_3^{4-}$. At higher pHs and in carbonate-free water, cationic hydroxide complexes can be formed: UO_2OH^+, $(UO_2)_2(OH)_2^{2+}$, and $(UO_2)_3(OH)_5^+$.

Usually, uranium levels in water and other environmental samples are measured and reported only in terms of total uranium by mass, without specification of either the chemical form(s) or the relative abundance of the isotopes present. The majority of the occurrence and exposure data used in this analysis involved the measurement and reporting of total uranium by mass. To estimate the corresponding radioactivity for these data, it was necessary to apply an "activity-to-mass" conversion factor. Frequently, a conversion factor of 0.68 pCi/µg is used to estimate the activity of uranium in a sample that has been measured as total uranium by mass. This factor is obtained using the assumption that the three isotopes are present at levels corresponding to the crustal abundance percentages noted previously. As discussed in detail in the previous uranium occurrence report (WMA 1990) and elsewhere (e.g., Hess et al. 1985; Longtin 1990), that assumption does not appear to be valid for uranium in water, where natural geochemical and radiological processes alter those proportions in favor of a slightly higher abundance of uranium-234 relative to uranium-238. This in turn results in a higher ratio than 0.68 pCi/µg because of the shorter half-life of uranium-234.

As discussed in WMA (1990), a review of isotope-specific data for 285 drinking water samples in the Nationwide Radon Survey (EPA 1985) as well as approximately 70 drinking water samples from the National Inorganics and Radionuclides Survey (NIRS) suggested that the activity-to-mass ratio in drinking water can be substantially higher than 0.68 pCi/µg, as much as 10 pCi/µg or more. However, it was observed that all of the high values occurred in those samples where the total amount of uranium mass was relatively low, that is, less than 5 µg/L, with the very highest values occurring where the total uranium present was less than 0.5 µg/L. For samples where uranium exceeded 5 µg/L, the ratio ranged only from about 0.7 to 2.1 pCi/µg. The mean and median values for the ratio for sites having more than 5 µg/L of uranium in the Nationwide Radon Survey were both 0.9 pCi/µg, with an approximate upper 95th percentile value of 1.3 pCi/µg. Similar values were seen for the NIRS data for samples having more than 5 µg/L.

Recognizing the uncertainty in estimating uranium activity levels from mass measurements in drinking water samples, two sets of occurrence estimates are presented here for uranium activity levels. The first set, called the "best estimate," was obtained by applying a conversion factor of 0.9 pCi/µg. The second set, referred to as the "conservative estimate," was obtained by applying a conversion factor of 1.3 pCi/µg.

3. Sources of Drinking Water Occurrence Information

The primary source of recent information on the occurrence of uranium in the nation's public drinking water supplies is the National Inorganics and Radionuclides Survey (NIRS) conducted by the EPA Office of Drinking Water's Technical Support Division between 1984 and 1986. NIRS was designed specifically to obtain representative national occurrence data for ground water supplies on 36 inorganic substances and 4 radionuclides, including uranium, to support the development and impact assessment of national primary drinking water regulations.

Longtin (1988, 1990) has provided an overview of NIRS, as well as a general summary of the results obtained for uranium and the other radionuclides. In brief, the NIRS sampling program was designed to reflect the national distribution of community ground water supplies by size of population served as inventoried by the Federal Data Reporting System (FRDS). The FRDS data was stratified into the following four population-size categories: very small (serving 25 to 500), small (serving 501 to 3,300), medium (serving 3,301 to 10,000), and large/very large (serving >10,000). A total of 1,000 sites were selected randomly from the FRDS data in proportion to the four size categories. Approximately 2.1 percent of the supplies in each size category were chosen for sampling. Of the 1,000 targeted sites, 990 were actually sampled in the NIRS. Uranium data were available for 976 sites.

In NIRS, total uranium was analyzed by mass using EPA method 908.2 (laser-induced fluorometry), with a Minimum Reporting Level (MRL) of 0.08 µg/L. (A small subset of duplicate samples were also analyzed for specific isotopes.)

Table II-3 provides a summary of the NIRS results. As shown there, uranium was measured at or above the MRL in 704 of the 976 NIRS sites for which uranium data were available. Longtin (1988) reported the mean value for those samples containing detectable uranium to be 2.55 µg/L, with a standard deviation of 6.93. The overall mean uranium concentration was calculated three ways, treating values reported as less than the MRL as equal to the MRL, one-half the MRL, and zero, respectively. The values for these three calculations were 1.86 µg/L, 1.85 µg/L, and 1.84 µg/L, respectively. Longtin (1988) reported the median of the positive values only to be 0.525 µg/L; the overall median value was determined to be 0.24 µg/L. A maximum concentration of 88.2 µg/L was reported, and only four sites were found to have levels above 50 µg/L.

Table II-3

Summary of Uranium Occurrence Results from the National Inorganics and Radionuclides Survey

System Size (Population Served)	Total Systems Sampled in NIRS[1]	Number of Systems with Concentration (μg/L) of:					
		≥0.08	>10	>20	>40	>50	>80
Very Small							
25-100	330	241	15	11	5	3	1
101-500	332	236	11	7	2	1	0
Small							
501-1,000	113	73	1	0	0	0	0
1,001-3,300	119	90	4	1	0	0	0
Medium							
3,301-10,000	54	43	0	0	0	0	0
Large/Very Large							
10,001-25,000	22	17	0	0	0	0	0
25,001-50,000	3	2	0	0	0	0	0
50,001-75,000	2	1	0	0	0	0	0
75,001-100,000	0	0	0	0	0	0	0
100,001-500,000	1	1	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	976	704	31	19	7	4	1

[1] Includes only those sites from which uranium data are available.

As noted above, NIRS involved the sampling of public ground water supplies; NIRS did not include any samples of surface water supplies. Unfortunately, there are no available data sets on uranium in surface water comparable to the NIRS data for ground water. One set of data that is available that provides some insight to uranium levels in surface waters is that provided by Oak Ridge National Laboratory (ORNL 1981). The ORNL report provides a summary of uranium in U.S. water compiled from approximately 90,000 samples obtained primarily through the National Uranium Resource Evaluation (NURE) program, with additional data from older water supply studies, such as the study of the 100 largest U.S. cities in the early 1960's reported by Durfor and Becker (1964). These data indicate that surface water (not limited to drinking water) had an overall range of uranium values of 0.015 to 856 µg/L with a median range of 0.15 to 0.29 µg/L. For ground water (again, not limited to drinking water), the overall range reported was 0.015 to 960 µg/L, with a median range of 0.29 to 0.74 µg/L. These data suggest that uranium levels are typically lower in surface water than in ground water.

4. Methodology and Assumptions

The estimates of the number of public drinking water supplies exceeding various uranium levels presented in section D.5 were obtained from probability distributions derived from the NIRS data. Separate lognormal distributions were developed for each of the four major size strata used in the original NIRS sample design. As described by Longtin (1988; 1990), probability plots of the NIRS results for uranium showed that the data were consistent with the assumption of a lognormal distribution for the data.

A log regression procedure was employed to estimate the parameters (i.e., the log mean and log standard deviation) for each of the four distributions. In this procedure, a simple linear regression analysis was performed (separately for each strata) using the ith ordered natural logarithm of the observed uranium concentration for the noncensored data as the dependent variable, and the ordered values obtained from the inverse of the standard normal distribution of i/(n+1) as the independent variable. (Note: Noncensored data are those with values above the MRL; censored data are those reported as less than the MRL.) The form of the linear regression function used is as follows:

$$y_{(i)} = \hat{\mu} + \hat{\sigma} F^{-1}[i/(n+1)]$$

where:

$y_{(i)}$ = the ith ordered natural logarithm of a noncensored uranium activity level from n values containing n_A censored and n_B noncensored values ($n = n_A + n_B$),

F^{-1} = inverse of the cumulative standard normal distribution function

$\hat{\mu}$ = intercept estimate from regression model

$\hat{\sigma}$ = slope estimate from regression model

The values for $\hat{\mu}$ and $\hat{\sigma}$ thus derived serve as estimates of the log mean and log standard deviation parameters, respectively, of the lognormal distribution. Table II-4 presents these values obtained for each strata for uranium.

These values can be used to estimate the probability of exceeding any specified uranium concentration "X" within each stratum from the following:

$$P_{(>X)} = 1 - F\{[\ln(X) - \hat{\mu}] / \hat{\sigma}\}$$

where:

$P_{(>X)}$ = Probability of exceeding any specified uranium concentration

F = cumulative standard normal distribution function

$\hat{\mu}, \hat{\sigma}$ = intercept and slope estimates, respectively, from the regression model described above

The estimate of the number of systems within each stratum exceeding the concentration "X" is then obtained by multiplying the above-computed probability by the number of supplies nationally in that stratum.

To estimate the number of systems exceeding specified activity levels, the log mean parameters in the model were transferred to reflect the assumed activity to mass ratio of 0.9 pCi/µg for the "best estimate" and 1.3 pCi/µg

Table II-4
Summary Statistics from the Log Regression Analysis of Uranium

System Size Strata	Number of Observations	Number of Censored Observations	Number of Non-censored Observations	Log Mean (μ)	Log Standard Deviation (σ)
Very Small	663	186	477	-1.361859	2.192172
Small	232	69	163	-1.384274	2.080586
Medium	53	10	43	-1.271301	1.730752
Large/Very Large	28	7	21	-1.562090	1.472605
Total	976	272	704		

for the "conservative estimate." (The log standard deviation parameter did not require transformation.)

In addition to providing a point estimate of the number of systems in each stratum exceeding an activity level of "X", upper and lower 95 percent confidence intervals were also constructed as follows:

$$\left(\sum_{X} N_x \bullet \hat{p}_x\right) \pm 1.96\left\{\sum_{X} N_x^2 \bullet \left[\hat{p}_x(1-\hat{p}_x)/(n_x-1)\right]\right\}^{1/2}$$

where

X = system size strata: very small, small, medium, or large/very large

N_x = the number of systems for the X^{th} stratum

$\hat{p}_x$ = estimated probability of exceeding a specified MCL alternative

n_x = the number of noncensored values used for the specified system size strata regression

Because there were no surface water data available from which occurrence probability distributions could be derived specifically for surface water systems, the national estimates of occurrence for surface water were obtained by applying the probability distribution functions derived from NIRS for ground water systems to the universe of surface water supplies within each stratum. It is recognized that this approach overestimates uranium occurrence in surface water systems.

As noted previously, the occurrence estimates are provided both in terms of the number of systems expected to exceed certain concentrations (µg/L) and activity levels (pCi/L). The model can be used to estimate occurrence above any specified level. The concentrations chosen to display the data in the table, correspond to the range of MCL alternatives being considered by EPA. Of particular mote is the value of 20 µg/L, which is the MCL value likely to be proposed. The activity levels used, 1.69, 16.9 and 169 pCi/L, correspond to current estimates of the 10^{-6}, 10^{-5} and 10^{-4} individual lifetime cancer risk levels.

5. National Occurrence Estimates

The estimated cumulative number of ground water supplies having uranium levels exceeding various concentrations of interest are presented by system size in Table II-5 for community ground water supplies and Table II-6 for non-transient non-community ground water supplies. The model predicts that approximately 957 community and 442 non-transient non-community ground water supplies will have uranium concentrations above 20 µg/L. Tables II-7 and II-8 provide the occurrence estimates by activity level. The "best estimate" indicates, that 7,995 community ground water supplies have activity levels exceeding the 10^{-6} risk level of 1.69 pCi/L, with 50 supplies exceeding the 10^{-4} risk level of 169 pCi/L. The corresponding "conservative estimates" for these levels are 10,196 systems and 86 systems, respectively.

The estimated cumulative number of surface water supplies having uranium levels exceeding the indicated concentrations are presented by system size for community supplies in Table II-9 and for non-transient non-community supplies in Table II-10. The model predicts that approximately 78 community and 11 non-transient non-community surface water supplies will have uranium levels above 20 µg/L. Tables II-11 and II-12 provide the surface water system occurrence estimates in terms of activity levels. The "best estimate" assumptions indicate that 844 community surface water supplies have uranium activity levels exceeding the 10^{-6} risk level of 1.69 pCi/L, but only four systems exceed the 10^{-4} risk level of 169 pCi/L. The corresponding "conservative estimates" are 1,123 systems and six systems, respectively.

As noted previously, the surface water occurrence estimates presented here are based on the probability distributions derived from the NIRS ground water data and are recognized to overestimate occurrence levels.

Table II-5
Estimated Cumulative National Occurrence of Uranium in Community Ground Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of Systems in the U.S.[2]	Number of Systems with Concentrations (μg/L) of: >0.08	>10	>20	>40	>50	>80
Very Small							
25-100	17079	11994	808	400	181	138	75
101-500	15354	10783	726	360	163	124	67
Small							
501-1,000	5038	3569	192	89	37	27	14
1,001-3,300	5185	3673	198	91	38	28	14
Medium							
3,301-10,000	2308	1767	45	16	5	3	1
Large/Very Large							
10,001-25,000	823	612	4	1	0	0	0
25,001-50,000	278	207	1	0	0	0	0
50,001-75,000	77	57	0	0	0	0	0
75,001-100,000	17	13	0	0	0	0	0
100,001-500,000	39	29	0	0	0	0	0
500,001-1,000,000	4	3	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	46202	32707	1974	957	424	320	171
Lower Bound[3]		31147	1280	465	96	34	0
Upper Bound		34265	2672	1446	754	607	383

1. Based on the NIRS data
2. Number of systems based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table II-6
Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Ground Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of Systems in the U.S.[2]	Number of Systems with Concentrations (µg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	13899	9761	657	325	147	112	61
101-500	3964	2784	188	93	42	32	17
Small							
501-1,000	1151	815	44	20	8	6	3
1,001-3,300	205	145	8	4	2	1	1
Medium							
3,301-10,000	49	38	1	0	0	0	0
Large/Very Large							
10,001-25,000	4	3	0	0	0	0	0
25,001-50,000	11	8	0	0	0	0	0
50,001-75,000	6	4	0	0	0	0	0
75,001-100,000	2	1	0	0	0	0	0
100,001-500,000	7	5	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	19298	13564	898	442	199	151	82
Lower Bound[3]		12825	555	198	34	7	0
Upper Bound		14304	1241	686	365	296	189

1. Based on the NIRS data
2. Number of systems based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table II-7
Estimated Cumulative National Occurrence of Uranium in Community Ground Water Supplies: By Uranium Activity[1]

System Size (Population Served)	Number of Systems with Activity Levels (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	3104	3917	428	625	22	38
101-500	2791	3522	385	562	20	34
Small						
501-1,000	839	1080	96	145	4	7
1,001-3,300	863	1111	99	150	4	7
Medium						
3,301-10,000	314	433	17	31	0	0
Large/Very Large						
10,001-25,000	56	89	1	2	0	0
25,001-50,000	19	30	0	1	0	0
50,001-75,000	5	8	0	0	0	0
75,001-100,000	1	2	0	0	0	0
100,001-500,000	3	4	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	7995	10196	1026	1516	50	86

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/μg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/μg conversion factor

Table II-8
Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Ground Water Supplies: By Uranium Activity[1]

System Size (Population Served)	Number of Systems with Activity Levels (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Guess[2]	Conservative[3]	Best Guess	Conservative	Best Guess	Conservative
Very Small						
25-100	2526	3188	348	509	18	31
101-500	721	909	99	145	5	9
Small						
501-1,000	192	247	22	33	1	2
1,001-3,300	34	44	4	6	0	0
Medium						
3,301-10,000	7	9	0	1	0	0
Large/Very Large						
10,001-25,000	0	0	0	0	0	0
25,001-50,000	1	1	0	0	0	0
50,001-75,000	0	1	0	0	0	0
75,001-100,000	0	0	0	0	0	0
100,001-500,000	0	1	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	3481	4400	473	694	24	42

1.. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/μg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/μg conversion factor

Table II-9

Estimated Cumulative National Occurrence of Uranium in Community Surface Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of Systems in the U.S.[2]	Number of Systems with Concentrations (μg/L) of: >0.08	>10	>20	>40	>50	>80
Very Small							
25-100	833	585	39	20	9	7	4
101-500	779	547	37	18	8	6	3
Small							
501-1,000	754	534	29	13	6	4	2
1,001-3,300	1040	737	40	18	8	6	3
Medium							
3,301-10,000	1156	885	23	8	2	2	1
Large/Very Large							
10,001-25,000	569	423	2	1	0	0	0
25,001-50,000	328	244	1	0	0	0	0
50,001-75,000	157	117	1	0	0	0	0
75,001-100,000	108	80	0	0	0	0	0
100,001-500,000	175	130	1	0	0	0	0
500,001-1,000,000	43	32	0	0	0	0	0
>1,000,000	15	11	0	0	0	0	0
Total	5957	4325	173	78	33	25	13
Lower Bound[3]		3989	86	24	0	0	0
Upper Bound		4662	261	133	66	53	32

1. Based on the NIRS data
2. Number of systems based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table II-10

Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of Systems in the U.S.[2]	Number of Systems with Concentrations (μg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	298	209	14	7	3	2	1
101-500	151	106	7	4	2	1	1
Small							
501-1,000	27	19	1	0	0	0	0
1,001-3,300	19	13	1	0	0	0	0
Medium							
3,301-10,000	7	5	0	0	0	0	0
Large/Very Large							
10,001-25,000	0	0	0	0	0	0	0
25,001-50,000	0	0	0	0	0	0	0
50,001-75,000	0	0	0	0	0	0	0
75,001-100,000	1	1	0	0	0	0	0
100,001-500,000	1	1	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	504	354	23	11	5	3	2
Lower Bound[3]		336	14	5	1	0	0
Upper Bound		373	32	18	9	8	5

1. Based on the NIRS data
2. Number of systems based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table II-11
Estimated Cumulative National Occurrence of Uranium in Community Surface Water Supplies: By Uranium Activity[1]

System Size (Population Served)	Number of Systems with Activity Levels (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	151	191	21	31	1	2
101-500	142	179	20	29	1	2
Small						
501-1,000	126	162	14	22	1	1
1,001-3,300	173	223	20	30	1	1
Medium						
3,301-10,000	157	217	9	15	0	0
Large/Very Large						
10,001-25,000	39	61	1	1	0	0
25,001-50,000	22	35	0	1	0	0
50,001-75,000	11	17	0	0	0	0
75,001-100,000	7	12	0	0	0	0
100,001-500,000	12	19	0	0	0	0
500,001-1,000,000	3	5	0	0	0	0
>1,000,000	1	2	0	0	0	0
Total	844	1123	85	129	4	6

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/µg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/µg conversion factor

Table II-12
Estimated Cumulative National Occurrence of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Uranium Activity[1]

System Size (Population Served)	Number of Systems with Activity Levels (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	54	68	7	11	0	1
101-500	27	35	4	6	0	0
Small						
501-1,000	4	6	1	1	0	0
1,001-3,300	3	4	0	1	0	0
Medium						
3,301-10,000	1	1	0	0	0	0
Large/Very Large						
10,001-25,000	0	0	0	0	0	0
25,001-50,000	0	0	0	0	0	0
50,001-75,000	0	0	0	0	0	0
75,001-100,000	0	0	0	0	0	0
100,001-500,000	0	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	89	114	12	19	0	1

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/µg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/µg conversion factor

III. Human Exposure

A. DRINKING WATER

The profile of population exposure to uranium in drinking water was obtained by combining the estimated number of public water supplies within each source and size strata exceeding various uranium levels presented in section II, with information from FRDS on the average number of people served by supplies in those strata. The resulting exposure estimates are provided in Tables III-1 through III-4 for the various categories of public water supplies.

In total, it is estimated that 718,000 people using public water supplies are exposed to uranium at levels exceeding 20 µg/L, with combined upper and lower 95 percent confidence bounds of 26,000 and 1,559,000. Most of the population predicted to have drinking water exposure above 20 µg/L are served by small and medium ground water supplies. As is the case with the occurrence estimates for surface water supplies, the population exposure estimates presented here are probably overestimate of exposure levels as a result of using ground water data as the basis for the surface water occurrence distributions.

Tables III-5 through III-8 provide estimates for each source and size category of the population expected to be exposed to drinking water with activity levels from uranium exceeding estimated individual lifetime risks ranging from 10^{-6} to 10^{-4}. The "best estimates" indicate that almost 20 million people are exposed to uranium above 1.69 pCi/L, associated with the 10^{-6} risk level, and that about 24,000 people are exposed above the 169 pCi/L. The corresponding "conservative" estimates for these risk levels are approximately 30 million and 42,000, respectively.

B. DIET

Comprehensive studies on radionuclides in food are not generally available. In recent years, the Food and Drug Administration (FDA) has included radionuclides in its Total Diet Studies or "Market Basket Surveys".

Table III-1
Estimated Cumulative Population (in thousands) Exposed to Uranium from Community Ground Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of People (in thousands)[2]	People (in thousands) Served by Systems with Concentrations (μg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	950	667	45	22	10	8	4
101-500	3850	2704	182	90	41	31	17
Small							
501-1,000	3910	2770	149	69	29	21	11
1,001-3,300	10000	7084	382	176	74	55	28
Medium							
3,301-10,000	13310	10192	259	91	28	18	7
Large/Very Large							
10,001-25,000	13110	9748	57	13	0	0	0
25,001-50,000	9540	7094	41	0	0	0	0
50,001-75,000	4770	3547	0	0	0	0	0
75,001-100,000	1360	1011	0	0	0	0	0
100,001-500,000	7600	5651	0	0	0	0	0
500,001-1,000,000	2760	2052	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	71160	52520	1115	461	182	133	67
Lower Bound[3]		44777	161	0	0	0	0
Upper Bound		60267	2071	937	445	354	217

1. Based on the NIRS data
2. Number of people based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table III-2
Estimated Cumulative Population (in thousands) Exposed to Uranium from Non-Transient, Non-Community Ground Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of People (in thousands)[2]	People (in thousands) Served by Systems with Concentrations (μg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	615	432	29	14	7	5	3
101-500	937	658	44	22	10	8	4
Small							
501-1,000	1015	719	39	18	7	6	3
1,001-3,300	351	249	13	6	3	2	1
Medium							
3,301-10,000	273	209	5	0	0	0	0
Large/Very Large							
10,001-25,000	71	53	0	0	0	0	0
25,001-50,000	275	204	0	0	0	0	0
50,001-75,000	398	296	0	0	0	0	0
75,001-100,000	180	134	0	0	0	0	0
100,001-500,000	1096	815	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	5211	3769	130	60	27	21	11
Lower Bound[3]		3364	80	26	4	0	0
Upper Bound		4174	182	95	50	43	26

1. Based on the NIRS data
2. Number of people based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table III-3

Estimated Cumulative Population (in thousands) Exposed to Uranium from Community Surface Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of People (in thousands)[2]	People (in thousands) Served by Systems with Concentrations (µg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	90	63	4	2	1	1	0
101-500	570	400	27	13	6	5	3
Small							
501-1,000	1280	907	49	23	9	7	4
1,001-3,300	4330	3067	165	76	32	24	12
Medium							
3,301-10,000	10200	7810	199	70	21	14	6
Large/Very Large							
10,001-25,000	12640	9399	55	12	0	0	0
25,001-50,000	15910	11830	69	0	0	0	0
50,001-75,000	10310	7666	45	0	0	0	0
75,001-100,000	10090	7502	0	0	0	0	0
100,001-500,000	36770	27341	160	0	0	0	0
500,001-1,000,000	22380	16641	0	0	0	0	0
>1,000,000	30090	22374	0	0	0	0	0
Total	154660	115000	773	196	69	51	25
Lower Bound[3]		88534	0	0	0	0	0
Upper Bound		141491	3000	525	229	181	109

1. Based on the NIRS data
2. Number of people based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table III-4
Estimated Cumulative Population (in thousands) Exposed to Uranium from Non-Transient, Non-Community Surface Water Supplies: By Total Uranium Concentration[1]

System Size (Population Served)	Number of People (in thousands)[2]	People (in thousands) Served by Systems with Concentrations (μg/L) of:					
		>0.08	>10	>20	>40	>50	>80
Very Small							
25-100	19	13	1	0	0	0	0
101-500	44	31	2	1	0	0	0
Small							
501-1,000	28	20	1	0	0	0	0
1,001-3,300	42	30	2	0	0	0	0
Medium							
3,301-10,000	53	41	0	0	0	0	0
Large/Very Large							
10,001-25,000	0	0	0	0	0	0	0
25,001-50,000	0	0	0	0	0	0	0
50,001-75,000	0	0	0	0	0	0	0
75,001-100,000	82	61	0	0	0	0	0
100,001-500,000	360	267	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0	0
Total	628	463	6	1	0	0	0
Lower Bound[3]		378	2	1	0	0	0
Upper Bound		548	8	2	1	1	1

1. Based on the NIRS data
2. Number of people based on FRDS
3. Lower and upper bounds based on 95 percent confidence intervals

Table III-5

Estimated Cumulative Population (in thousands) of Uranium in Community Ground Water Supplies: By Uranium Activity[1]

System Size (Population Served)	People (in thousands) Served by Systems with Concentration (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	173	218	24	34	1	2
101-500	2791	833	396	141	5	9
Small						
501-1,000	839	838	74	113	3	5
1,001-3,300	1665	2143	190	288	7	13
Medium						
3,301-10,000	314	2499	101	177	0	0
Large/Very Large						
10,001-25,000	895	1412	15	33	0	0
25,001-50,000	652	1027	0	24	0	0
50,001-75,000	326	514	0	0	0	0
75,001-100,000	93	146	0	0	0	0
100,001-500,000	519	818	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	7484	10498	500	810	16	29

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/μg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/μg conversion factor

Table III-6
Estimated Cumulative Population (in thousands) of Uranium
in Non-Transient, Non-Community Ground Water Supplies: By Uranium Activity[1]

System Size (Population Served)	People (in thousands) Served by Systems with Concentration (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	112	141	15	23	1	1
101-500	170	215	23	34	1	2
Small						
501-1,000	169	218	19	29	1	1
1,001-3,300	58	75	7	10	0	0
Medium						
3,301-10,000	37	51	0	4	0	0
Large/Very Large						
10,001-25,000	0	0	0	0	0	0
25,001-50,000	19	30	0	0	0	0
50,001-75,000	0	43	0	0	0	0
75,001-100,000	0	0	0	0	0	0
100,001-500,000	0	118	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	565	891	64	100	3	4

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/μg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/μg conversion factor

Table III-7
Estimated Cumulative Population (in thousands) of Uranium in Community Surface Water Supplies: By Uranium Activity[1]

System Size (Population Served)	People (in thousands) served by Systems with Concentration (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	16	21	2	3	0	0
101-500	104	131	14	21	1	1
Small						
501-1,000	213	162	24	37	1	2
1,001-3,300	721	928	82	125	3	6
Medium						
3,301-10,000	1387	1915	77	136	0	0
Large/Very Large						
10,001-25,000	863	1361	17	32	0	0
25,001-50,000	1087	1713	0	40	0	0
50,001-75,000	704	1110	0	0	0	0
75,001-100,000	689	1087	0	0	0	0
100,001-500,000	2511	3960	0	0	0	0
500,001-1,000,000	1528	2410	0	0	0	0
>1,000,000	2055	3240	0	0	0	0
Total	11878	18186	213	394	5	9

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/µg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/µg conversion factor

Table III-8
Estimated Cumulative Population (in thousands) of Uranium in Non-Transient, Non-Community Surface Water Supplies: By Uranium Activity[1]

System Size (Population Served)	People (in thousands) Served by Systems with Concentration (pCi/L) of:					
	>1.69		>16.9		>169	
	Best Estimate[2]	Conservative[3]	Best Estimate	Conservative	Best Estimate	Conservative
Very Small						
25-100	3	4	0	1	0	0
101-500	8	10	1	2	0	0
Small						
501-1,000	5	6	1	1	0	0
1,001-3,300	7	9	0	1	0	0
Medium						
3,301-10,000	7	10	0	0	0	0
Large/Very Large						
10,001-25,000	0	0	0	0	0	0
25,001-50,000	0	0	0	0	0	0
50,001-75,000	0	0	0	0	0	0
75,001-100,000	0	0	0	0	0	0
100,001-500,000	0	0	0	0	0	0
500,001-1,000,000	0	0	0	0	0	0
>1,000,000	0	0	0	0	0	0
Total	30	39	2	5	0	0

1. Based on the NIRS data
2. "Best Estimate" based on a 0.9 pCi/µg conversion factor
3. "Conservative" estimate based on a 1.3 pCi/µg conversion factor

The FDA's program monitors radionuclides in food supplies collected near nuclear power plants and selected imported foods. Data for uranium were rarely reported by the FDA for studies completed between 1978 and 1982. There are two other studies that address the dietary intake of uranium: Welford and Baird 1967, and Fisenne et al. 1987.

Welford and Baird of the U.S. Atomic Energy Commission investigated the uranium content of typical adults diets in 1967. The study focused on the diets of residents from New York City, Chicago, and San Francisco. The food categories and corresponding uranium intake levels are presented in Table III-9 for each of the three locations. The uranium content of the individual food groups were similar although in several cases the levels for the same food type varied geographically. Despite this, the daily uranium intake was found to be constant at the three study sites: 1.3 µg/day in New York City, 1.4 µg/day in Chicago, and 1.3 µg/day in San Francisco (Welford and Baird 1967).

Fisenne et al. (1987) examined the concentration of individual uranium isotope activities and other alpha emitting radionuclides in food for New York City diets of 1978. The food categories were similar to those investigated by Welford and Baird. The individual uranium isotope activities can be converted to uranium mass based on the respective decay rates (see Table III-9 for results). The daily intake of total uranium (i.e., all three isotopes) calculated to be 1.2 µg, which is in close agreement with the results of Welford and Baird.

Since the Welford and Baird study included three cities (New York, Chicago, and San Francisco), it was chosen as the basis for computing the average uranium dietary intake. In comparison, the Fisenne study supports the use of the Welford and Baird data. As seen in Table III-9, the estimates presented in the two studies agree well for total intake and, with a few exceptions, for individual food categories.

Data extracted from the Welford and Baird study were sent to the Center for Environmental Sciences, University of Colorado at Denver. The Center has developed a computer model to estimate dietary intakes using current data on

Table III-9
Uranium Dietary Intake Studies

	NYC: Fisenne (1987)							Welford and Baird (1967)			
Food Groups	U-234 (mBq/yr)	U-235 (mBq/yr)	U-238 (mBq/yr)	U-234 (ug/yr)	U-235 (ug/yr)	U-238 (ug/yr)	Total Uranium (ug/yr)	Uranium NYC (ug/yr)	Uranium S.F. (ug/yr)	Uranium Chicago (ug/yr)	ave Total U (NYC,SF,Chi) (ug/yr)
Fresh vegs	1128	58	1142	0.0050	0.73	92.39	93.13	25	25	44	31.3
Canned vegs	99	2.6	92	0.0004	0.03	7.44	7.48	4	2	4	3.3
Root vegs	125	1.3	77	0.0006	0.02	6.23	6.25	12	9.4	12	11.1
Potatoes	41	1.9	34	0.0002	0.02	2.75	2.77	111	101	101	104.3
Dry beans	93	4	83	0.0004	0.05	6.72	6.77	4.5	11	11	8.8
Fresh fruit	118	-2.2	118	0.0005	-0.03	9.55	9.52	76	76	42	64.7
Canned fruit	29	0.2	11	0.0001	0.00	0.89	0.89	4.2	6.4	4	4.9
Fruit juice	15	-0.9	17	0.0001	-0.01	1.38	1.36	1.1	1.1	3.4	1.9
Bakery prods	1305	56	1012	0.0058	0.71	81.88	82.59	66	58	58	60.7
Flour	159	8.5	164	0.0007	0.11	13.27	13.38	23	14	8.4	15.1
Whole grain	277	11	187	0.0012	0.14	15.13	15.27	16	16	16	16.0
Macaroni	11	0.3	11	0.0000	0.00	0.89	0.89	1.2	1.4	1.9	1.5
Rice	7.5	0.5	9	0.0000	0.01	0.73	0.73	5.8	18	4.3	9.4
Meat	145	1.3	184	0.0006	0.02	14.89	14.90	79	104	46	76.3
Poultry	15	1.3	16	0.0001	0.02	1.29	1.31	2.7	8.4	5.6	5.6
Eggs	15	0.5	28	0.0001	0.01	2.27	2.27	3.4	3.4	3.4	3.4
Fresh fish	145	3.3	105	0.0006	0.04	8.50	8.54	3.4	6.8	4.5	4.9
Shellfish	2200	90	1935	0.0097	1.14	156.55	157.70	9.5	29	31	23.2
Dairy prods	200	10	147	0.0009	0.13	11.89	12.02	16	31	62	36.3
Sum	6123	251	5372	0.03	3.12	434.6	437.8	463.8	521.9	462.5	482.7

Conversion Factors:

U-234	1 ug = 226,135 mBq
U-235	1 ug = 79.29 mBq
U-238	1 ug = 12.36 mBq

food consumption and the chemical composition of foods. The model is based on the USDA National Food Consumption Survey on dietary consumption of various food products among different age, sex, socio-economic, and geographic subsets of the U.S. population. The data for uranium, from the Welford and Baird study, was considered adequate by the Center for computing reasonable estimates of uranium content in food of the various categories. However, it should be emphasized that the estimates are based on a limited amount of data and, therefore, are not comprehensive in terms of the potential levels that may be found throughout the United States for any given food type (Meglan 1985).

The model provided estimates for uranium dietary intakes for four population groups: toddlers, children, adolescents, and adults. Uranium intake from drinking water is not accounted for in the model. The concentrations are presented for total uranium, as measured by Welford and Baird.

Data for males and females have been averaged together. After accounting for weight differences, intake values of uranium by males and females are not significantly different within a given food or age category. The uranium intake values from the three geographic sampling locations used in the evaluation (New York, Chicago, and San Francisco) have also been averaged. The results of the uranium intake model for each population group are summarized in Table III-10.

The daily intakes for the different age and sex categories for adults obtained from the University of Colorado model generally ranged from about 0.7 µg/day to 1.1 µg/day. Higher values were estimated for men than for women. The University of Colorado model intake estimates are slightly lower than the intakes reported by Welford and Baird. In the report provided by the University of Colorado, it is noted that the amounts of food consumed, as estimated in more recent USDA surveys, on which the model is based, were lower than the amounts found in earlier surveys. Welford and Baird used the 1955 USDA data on food consumption for their estimate, which may result in the difference in intake estimates.

Table III-10
Modeled Dietary Intake of Uranium

Population Group	Total Daily Intake (µg/day)	Major Contributing Food Categories and Concentrations (percentage of total) of Combined Uranium Intake (µg/day)				
Toddlers[1]	0.678	Potatoes 0.100 (14.7%)	Cereals 0.099 (14.6%)	Mixed Fruit 0.096 (14.2%)	Milk 0.090 (13.3%)	Legumes 0.078 (11.5%)
Children[2]	0.838	Potatoes 0.147 (17.5%)	Cereals 0.126 (15.0%)	Bakery 0.109 (13.0%)	Mixed Fruit/ Bread 0.085 (10.1%)	Milk/ Legumes 0.082 (9.8%)
Adolescents[3]	1.40	Potatoes 0.219 (15.6%)	Milk 0.211 (15.1%)	Bread 0.116 (8.3%)	Cereal/ Bakery 0.107 (7.6%)	Legumes 0.103 (7.4%)
Adults[4]	0.988	Potatoes 0.238 (24.1%)	Bread 0.112 (11.3%)	Cereals 0.104 (10.5%)	Legumes 0.087 (8.8%)	Mixed Fruit 0.085 (8.6%)

[1] 1- to 2-years old.
[2] 3- to 8-years old.
[3] 9- to 18 years old.
[4] Over 18 years old.
Study from Meglen (1985).

Overall, the total dietary intake estimated for uranium did not exceed 1.4 µg/day for any of the age groups. The adolescent group consisting of individuals between the ages of 9 and 18, had the highest overall uranium intake. Uranium intake was lowest for toddlers, being less than half of that determined for adolescents.

C. AMBIENT AIR

The review of available literature indicates that radioactive uranium isotopes are not common contaminants of ambient or indoor air. The uranium isotopes (primarily uranium-238) are solids and generally exist in air only in particulate form. Uranium predominantly binds to soil and, therefore, is not expected to be present in indoor air. Uranium in airborne dust appears to result from the re-suspension of soil and exhibits concentrations similar to those found in soil particles (NCRP 1987).

Direct measurement of ambient uranium is not common. However, measurements have been taken in New York City and at the Argonne National Laboratory in Illinois. The ambient concentrations of uranium were found to be 8 attoCuries/m^3 (aCi) in the air outside the Argonne National Laboratory. Welford and Baird (1967) reported a concentration of 250 aCi/m^3 uranium in New York City outdoor air, while Fisenne et al. (1987) reported 18 aCi/m^3. Converting these values to the more familiar units of pCi/L, results in uranium concentrations of 0.08×10^{-7} pCi/L for the Argonne Laboratory, and 0.18×10^{-7} and 2.5×10^{-7} pCi/L for New York City.

The available data indicate uranium is present in air only at extremely low levels. In comparison to water and dietary contributions, respiratory intake appears to be negligible. To illustrate this fact, consider an average ambient air uranium concentration of 0.2×10^{-7} pCi/L (NCRP 1987). Assuming a ventilation rate of 20 m^3/day, the respiratory intake of radioactive uranium would be only 0.0004 pCi/day.

D. TOTAL EXPOSURE AND RELATIVE SOURCE CONTRIBUTION

The total exposure and relative source contribution analyses are provided primarily to support the determination of the MCLG for drinking water contaminants. For carcinogens, EPA has established a policy of setting the MCLG at zero, which may apply to uranium if EPA sets the MCLG based on its radioactivity. However, since uranium is also of concern as a kidney toxin, EPA may set an MCLG based on those effects. To support that option, the total exposure and RSC analyses are provided in terms of total uranium intake, and are presented using units of mass, specifically µg/day.

The occurrence analysis and the available literature indicate that the predominant exposure routes for uranium are diet and drinking water. As seen in Section III.C, respiratory intake of ambient uranium is negligible; therefore, respiratory intake is ignored in this estimation of total exposure. Section D.1 summarizes the analytical approach used to estimate total exposure and relative source contribution (RSC), and Section D.2 presents the results of the analysis.

1. Analytical Approach

Using the information provided from NIRS, it is possible to develop a profile of population exposure and intake for uranium from drinking water. Similarly, the dietary data provided in Section III.A provide a general national profile of intake from food. However, these data sets do not specifically address the simultaneous intake from both sources. Absent specific data on total intake from multiple sources, it is possible to estimate it from the separate data sets using a Monte Carlo simulation approach.

The Monte Carlo analysis performed here, using "@Risk" software, computed the combined intake from drinking water and food (as well as the "percent contribution from drinking water") for a simulated random sample of 1,000 people selected from the overall population. This simulated sampling was performed as follows:

First, the United States population was stratified into four groups based on the category of water supply used. The four groups were:

Group:	Population	Relative Weight
Very small	5,460,000	0.024
Small	19,520,000	0.086
Medium	23,510,000	0.104
Large/very large	177,330,000	0.785

The probability of selecting an individual from any one of these categories is reflected by the relative weight for the group based on the total population served.

Once an individual was selected from one of these five groups, a drinking water intake value was calculated for that person. The drinking water intake was derived from the lognormal distributions of uranium levels in drinking water developed from NIRS for each of these categories as described in the preceding sections, and an assumed drinking water intake of 2 l/day.

Once a drinking water intake was determined for each individual in the sample, a food intake value was also computed. The data used for the food intake were from the Welford and Baird (1967) study as re-evaluated by Meglen (1985). Meglen estimated the mean daily intake values for several age/sex subpopulations for each of the three cities studies by Welford and Baird (i.e., New York, Chicago, and San Francisco). Using six adult male age groups for each of the three cities (i.e., 18 groups total), an overall mean and standard deviation were computed to be 0.934 µg/day and 0.069. These values were used as the parameters for an assumed normal distribution of food intake values. The Monte Carlo simulation selected a food intake value for each individual from that normal distribution.

2. Results

Total Uranium Exposure

Figure III-1 shows the distribution of total uranium exposure in a histogram form; summary statistics are provided in Table III-11. The

Figure III-1

Distribution of Total Uranium Exposure from Simulation Model

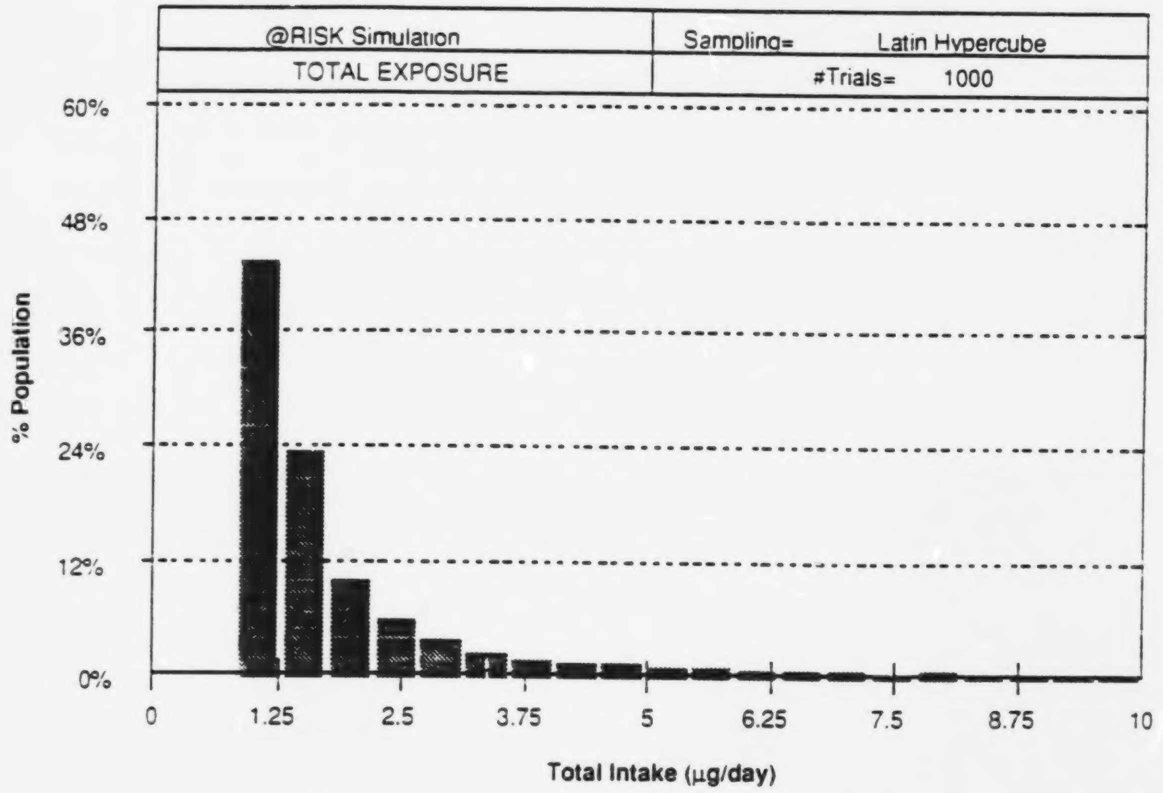

Table III-11
Summary Statistics for the Total Exposure Distribution for Uranium

Statistic	Value (µg/day)
Mean	3.42
Standard Deviation	26.6
Order Statistics:	
Minimum Result	0.82
10th Percentile	0.99
25th Percentile	1.09
50th Percentile (median)	1.37
75th Percentile	2.12
90th Percentile	4.11
Maximum Result	829

estimated mean intake is 3.4 µg/day, with a median value of 1.37 µg/day. The upper 95th percentile of intakes is estimated to be 4.1 µg/day.

Relative Source Contribution

The percentage contribution of drinking water to total uranium intake is shown in Figure III-2; the summary statistics are provided in Table III-12. As shown there, the "percent contribution from drinking water" ranges from 0.03 percent to 99.9 percent. The mean value is 36.6 percent, and the median value is 31 percent.

Figure III-2

Distribution of Drinking Water Contribution to Total Intake from Simulation Model

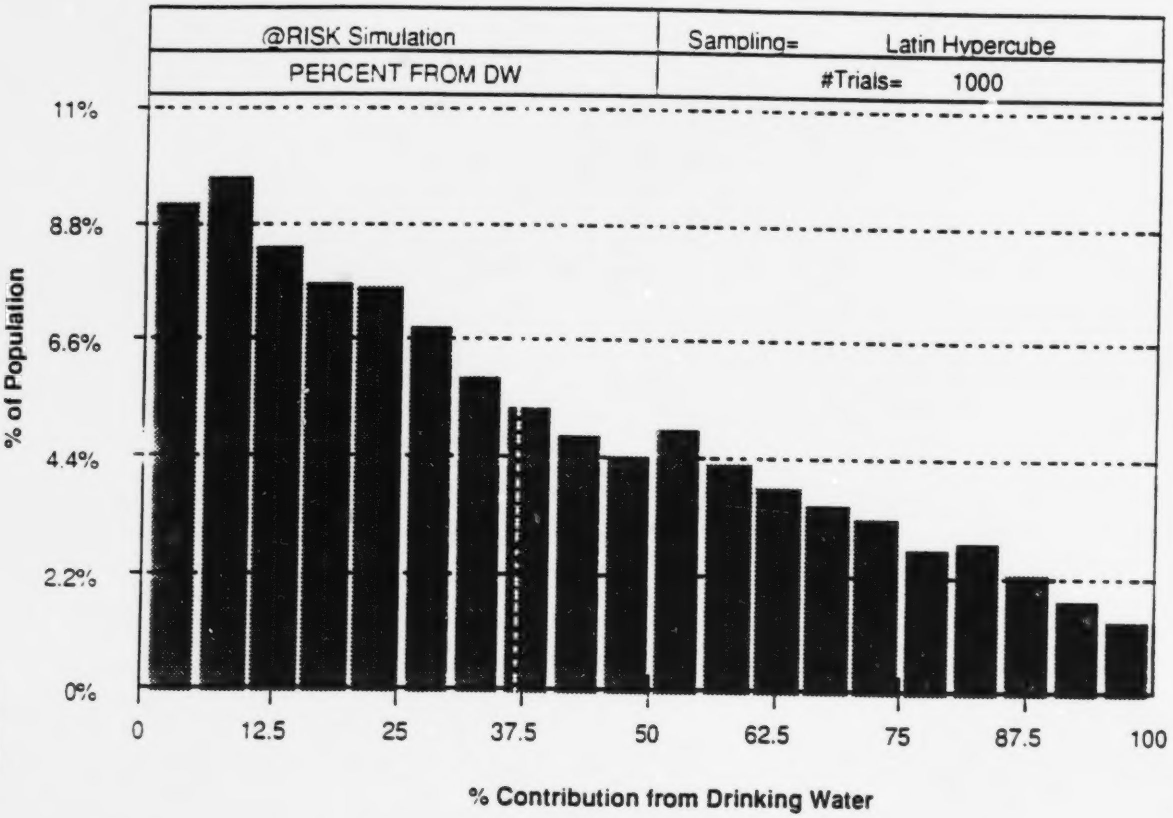

Table III-12
Summary Statistics for the Percent From Drinking Water Distribution for Uranium

Statistic	Value (µg/day)
Mean	36.6
Standard Deviation	26.3
Order Statistics:	
Minimum Result	0.37
10th Percentile	5.9
25th Percentile	13.8
50th Percentile (median)	31.0
75th Percentile	56.2
90th Percentile	76.2
Maximum Result	99.9

IV. TOXICOKINETICS

A. ABSORPTION

Data on the gastrointestinal absorption of uranium are available from both human and animal studies, for both acute and chronic periods. Data from acute human experiments are from studies of persons who have consumed either large amounts, or low, background amounts of uranium. Chronic studies are available which estimate levels of intake over a period of years. In some cases the authors have calculated absorption, in other cases authors of review articles have reevaluated the data, and in some cases, the reevaluations of the data have been made within this document.

There are several ways to calculate gastrointestinal absorption factors for uranium. It is well known that uranium absorbed from the gastrointestinal tract is excreted almost exclusively in the urine, and the amount in feces is generally the amount which is not absorbed. One way to calculate minimum absorption is to use urinary excretion divided by the amount of intake. Absorption can also be calculated from the fraction of uranium which is not excreted in the feces, or (100 percent - (amount in feces/amount of intake)). Levels remaining in various body tissues (bone, kidney, muscle, or whole body) at time of autopsy have also been used as an estimate of absorption levels. Alternatively, absorption can be calculated by a linear regression method, with absorption equal to the slope of the line between the amount measured in the urine and the amount of intake in the water (Spencer et al. 1990).

Table IV-1 summarizes absorption data from human studies. This table indicates that absorption, calculated by urinary excretion, ranges from 0.57 to 1.6 percent of intake. Using the fecal excretion method of calculation, absorption levels are calculated to be 26 percent of intake. Using the linear regression method, the absorption level is calculated to be about 5 percent.

Table IV-2 summarizes calculations of absorption factors from data in animals. This table shows that absorption factors for acute studies in rats, mice, hamsters, dogs and baboons range from 0.01 to 2.8 percent. The highest value (2.8 percent) is associated with a very high gavage dose. No species

Table IV-1
Calculation of Oral Absorption Fractions in Humans for Uranium

Percent Absorbed	Method of Calculation	Author
ACUTE STUDIES		
0.3-3	urine excretion	Hursh et al. 1969
0.7	urine excretion	Butterworth 1955
0.57	urine excretion	Wrenn et al. 1989
1.8	urine excretion	Spencer et al. 1990
5.2	linear regression of urine excretion data	Spencer et al. 1990
CHRONIC STUDIES		
0.7	urine excretion	Welford and Baird 1967
1.6-0.7	urine excretion	Masuda 1971a,b,c,d
3.8	urine excretion	Somayajulo et al. 1980
1.8	urine excretion	Spencer et al. 1990
1	urine excretion	Singh et al. 1990
26	fecal excretion	Somayajulo et al. 1980
26	fecal excretion	Spencer et al. 1990
31	estimated urine excretion	Hamilton 1972, as calculated by Hursh and Spoor 1973
12	estimated intake	Welford and Baird 1967 as as calculated by Hursh and Spoor 1973
7.7	estimated intake	Welford and Baird 1967 as as calculated by Wrenn et al. 1985

Table IV-2
Calculation of Oral Absorption Fractions in Animals for Uranium

Percent Absorbed	Species	Measured Levels of Uranium in:	Reference
ACUTE			
0.05	rat	urine, bone, liver	Hamilton 1948
0.35	rat	urine, bone, liver	Reanalysis by Durbin and Wrenn 1975
0.06	rat	urine, bone, liver	Sullivan 1980
0.01	rat	bone, liver, kidney	Sullivan et al. 1983
0.067	rat (fed)	bone, liver, kidney	Sullivan et al. 1986a
0.174	rat (fasted)	bone, liver, kidney	Sullivan et al. 1986a
0.6–2.8	rat	urine, bone, kidney	LaTouche et al. 1987
0.77	hamster	bone, liver, kidney	Harrison and Stather 1981
1.55	dog	urine, feces	Fish et al. 1960
1.2	baboon (fasted)	urine, feces	Larsen et al. 1984
0.51	baboon (fed)	urine, bone	Bhattacharyya et al. 1989
4.5	baboon (fasted)	urine, bone	Bhattacharyya et al. 1989
0.069	mice (fed)	urine, whole body	Bhattacharyya et al. 1989
0.80	mice (fasted)	urine, whole body	Bhattacharyya et al. 1989
CHRONIC			
0.035	rat	kidney, bone	Tracy et al. 1983
0.28	rabbit	kidney, bone	Tracy et al. 1983
0.1	rat	bone	Maynard et al. 1953
0.04	rat	bone	Recalculation of above by Wrenn et al. 1985

seems to be substantially different than the others. Additional data show that absorption in fasted animals is slightly greater than in fed animals, but that even these absorption levels are low. Chronic studies in rats and rabbits also show low absorption values of 0.035 to 0.28 percent.

The solubility, and thus the absorption, of uranium is dependent on its valance state. Uranium^{+4} and uranium^{+6} are the only valence states stable in solution. Most uranium^{+4} compounds are insoluble. Although injected uranium^{+4} complexes can exist for a short time in serum, uncomplexed uranium^{+4} compounds are significantly hydrolysed at pH 7.4 and they are poorly absorbed (Durbin 1984). Water soluble hexavalent compounds include uranyl nitrate hexahydrate, uranyl acetate and UO_2F_2. In biological fluids, the principal ion, uranyl (UO_2^{++}), is often complexed to HCO_3^-, citrate ion or proteins. The uranyl ion is the principal form of uranium that is absorbed and transported.

1. Humans

Various absorption factors have been calculated for uranium. Absorption has ranged from 0.7 to 31 percent depending on the method of calculation. A reasonable mid-range estimate of the amount of uranium absorbed by humans during a lifetime of exposure is about 5 percent of the intake. When used in a pharmacokinetic model, this provides an f_1 value of 0.05. Uncertainties associated with this value include variations between individuals, low numbers of individuals studied, and effects of fasting or low iron intake.

Acute

Four men were administered 10.8 mg uranium as uranyl nitrate (0.08 to 0.17 mg uranium/kg) in 100 mL of Coca Cola, and levels of radioactivity were measured in the urine for 9 to 15 days (Hursh et al. 1969). Urine content of uranium indicates that the amount absorbed was 0.3, 0.7 , 1.1, and 3 percent of the intake for the four men. A small amount of the absorbed dose was probably also retained in the skeleton. Uranium in feces was also measured for two of the men. The cumulative excretion for 9 days was 99.7 percent in one and 91.8 percent in the other. Since the second subject had one missing sample, the only reliable data are from one man who retained 0.3 percent of the administered dose for more than 9 days. This man excreted most (86 percent) of the administered dose in the feces within 2 days. Hursh concludes that it is reasonable to assume that the average absorption of soluble uranium by man lies between 0.5 and 5 percent of the ingested dose. The data suggest that the absorption range is from 0.3 to 3 percent. In two cases the curve of urinary excretion was still rising rapidly on the last day of measurement. (These data were presented as three pages of notes in a journal, and were probably not peer reviewed).

Butterworth (1955) administered 0.47 g of uranium (6.7 mg/kg) to one man who then had diarrhea and vomited profusely so that the intake cannot be accurately assessed. The subject excreted 2.5 mg uranium in the urine within a week. The authors calculated the absorption factor to be 0.73 percent, but this number cannot be considered to be reliable.

Urine and feces from 12 volunteers were collected for 7 days for background measurements of uranium (Wrenn et al. 1988, 1989; Singh and Wrenn 1987). The subjects then were to drink 900 mL of water containing 90 pCi of uranium-238 and 90 pCi of uranium-234 (273 µg uranium), but intake was not measured, and urine and feces were analyzed for 7 more days. Uranium in the food or tap water was not measured. Exact data on urinary excretion were not provided and data on fecal excretion were not provided. However, most of the uranium ingested was excreted in the feces 2 days after ingestion of the water. The data for urinary excretion for ten subjects were provided. The authors calculated the percentage of uranium absorbed as:

$$\frac{\text{net urinary excretion over background for 3 days}}{\text{uranium in water x } 1/0.79},$$

where 0.79 is the fraction of the absorbed uranium which is expected to be excreted within 3 days. The average absorption was thus 0.575 percent for uranium-238 and 0.585 percent for uranium-234. However, there was variation among the subjects; 60 percent of the subjects excreted less than 0.2 percent of the administered uranium in the urine.

The uranium intake and excretion of four men was studied in a metabolic research unit for 24 to 54 days (Spencer et al. 1990). Average daily uranium levels in food were found to be 0.74 µCi uranium-234 and 0.53 µCi uranium-238, in milk they were 0.008 μCi uranium-234/L and 0.009 μCi uranium-238/L and in water they were 0.28 μCi uranium-234 and uranium-238. Total daily intake was 0.95 to 1.8 μCi/day for uranium-234 and 0.65 to 1.24 μCi/day for uranium-238. Uranium levels in urine and feces were also determined. Average urinary excretion was 1.8 percent of uranium-234 and 1.5 percent of uranium-238 intake. The average net absorption (100 - (total excretion/total input)) was 26 percent for uranium-234 and 23 percent for uranium-238. Another method of analysis is the regression model which fits the excretion and intake data to the linear equation $Y = 0.052\ X - 0.18$ where Y = the amount of uranium-234 excreted in the urine per day, and X = the amount of uranium-234 consumed in water per day. For uranium-238 the slope is 0.04. The data used in these equations were obtained from the four test subjects as well as from four laboratory personnel who drank ordinary New York City tap water at an average consumption of 0.04 μCi per day for uranium-234.

Chronic

Uranium in sample foods was measured from an unspecified location in the United States (Welford and Baird 1967). They estimated personal uranium intake in New York, Chicago and San Francisco based on U.S. Department of Agriculture reports of standard food consumption in those cities. These levels were 464, 523, and 463 μg uranium/yr for the three cities, or 1.3 μg uranium/day. The mean uranium level in tap water in New York was found to be 0.032 μg uranium/L. The measurement of uranium in air samples in New York City revealed an average concentration of 0.4 ng/m^3, and this low level was considered to be too small to account for any uranium absorbed into the body. The average concentration of uranium levels in bone was 0.20 μg uranium/g of ashed bone, and 11 lung samples revealed an average concentration of 0.001 μg uranium/gram of wet lung tissue. The human tissue was first identified as being from New York, but was later found to have been from an area in the mid-western part of the United States, known to have elevated levels of uranium in the drinking water (Fisenne and Welford 1986). The uranium levels in urine in 11 samples from Chicago averaged 0.009 μg uranium/L. Assuming water intake of 2 L/day, total intake can be estimated to be 1.3 μg from food plus 0.64 μg uranium from water for a total of 1.94 μg uranium/day. Excretion in urine is 0.009 μg uranium/L for 1.5 L or 0.01 μg/day. Absorption can be calculated to be 0.01/1.94 = 0.7 percent.

Wrenn et al. (1985) also used these data to calculate gastrointestinal absorption. Using an estimate of intake of 1.75 µg uranium/day (obtained utilizing the data from Welford and Baird 1967) and urinary excretion of 0.097 µg uranium/L x 1.4 L (ICRP 1975) or 0.135 µg uranium/L, they calculated an absorption factor of 7.7 percent. Hursh and Spoor (1973) reevaluated the data provided by Welford and Baird (1967) and Welford et al. (1970). The Welford et al. (1970) data were presented as preliminary results during Conference Proceedings and have apparently never been published or peer reviewed. Hursh and Spoor (1973) estimated absorption to be 12 percent, which was calculated by dividing the estimated total urinary excretion (0.154 µg) by the estimated total dietary intake (1.3 µg).

In another set of studies, Masuda (1971a,b,c,d) measured urinary excretion in residents of three villages near a uranium mine in Japan. The urinary excretion ranged from nondetectable to 0.24 µg/day, as compared to nondetectable to 0.04 µg/day in a control village, with means of 0.15, 0.07 and 0.3 for the three exposed villages, and 0.006 for the control village. The dietary uranium intake was 3.9, 5.6, and 9.1 µg/day/person in the three experimental villages, as compared to 1.8 in the control village. The ratio of urinary excretion to intake (indicating absorption) was 1.61, 1.32, and 0.69 percent in the exposed areas, and 0.34 percent in the control area. Levels of uranium in the water were not given, nor were levels of uranium in feces.

Uranium levels were measured in ten drinking water supplies in the city of Ahmedabad, India (Somayajulu et al. 1980). They also measured uranium in food in a cafeteria where one man usually ate and measured the uranium content of his urine and feces. The number of days of collection is not clearly presented, but is presumably 1 to 3 days. The amount of uranium in the blood of this man was not presented, but the amount in the blood of a man who presumably consumed about the same amount of uranium was presented as 13.3 µg uranium/L of blood. Since the duration of urine and feces collection was not well presented, an accurate estimate of the percentage absorbed or retained cannot be made. Input was about 3 L x 20 µg/L (60 µg) in water plus 0.02 ppm in food x 1 kg of food = 0.02 mg (20 µg). Total input was about 80 µg/day. Output = 1.125 L of urine x 2.0 µg/L + 219 g of feces x 0.26 µg/g = 2.25 + 56.94 = 59.19 µg. 59/80 = 74 percent eliminated in 1 day, for an absorption factor of 26 percent. Another way to calculate the percent absorbed (used by Wrenn et al. [1985]) would be to divide urinary excretion by total excretion (2.25/(2.25 + 56.9) for an absorption factor of 3.8 percent. Only one subject was tested and input and output numbers are reasonable estimates, but should not be considered to be accurate measurements.

Hamilton (1972) measured uranium content of sampled foods in the United Kingdom as well as in 1 to 8 samples of muscle, fat, liver and heart, 21 samples of blood and 63 samples of ashed bones of various types. Using an estimate of the total weight of the tissue in a normal man, the total amount of uranium in these tissues was estimated to be 86.3 µg uranium. The total amount of uranium in the body was estimated to be about 125 µg. Using the amount of uranium contained in the sample foods, and estimating the daily European diet, the total intake of uranium in the food was estimated to be about 0.99 µg uranium/day. The amount of uranium in the water was not measured or estimated. Using these levels (and calculating daily dietary intake to be 1.2 µg) and levels of daily urinary excretion of 0.38 µg (Dean 1967), Hursh and Spoor (1973) calculated absorption to be 31 percent. Since the data by Dean have apparently never been published, this estimate cannot be verified.

Uranium in feces and urine was measured in 12 subjects for 7 days (Singh et al. 1990). The daily excretion was highly variable within and among subjects. The average daily excretion was 4.4 µg uranium/day in the urine. Data for fecal excretion were not completely presented. Average values, or values for all 12 subjects were not presented. Authors state that urinary excretion was 1 percent of total excretion. Drinking water samples were measured to have an average of 1.46 µg uranium/L. Authors did not directly measure amount of uranium in food in consumed, but estimated the levels, based on excretion data.

Novikov and Rezanov (1962) studied 14 children who drank water containing an unusually high amount of uranium as compared to 11 children who drank lower amounts. The investigators measured uranium in urine and feces, but could account for only 1 percent of the apparent ingested dose. Food intake and assay methods were not reported. The reliability of this study is questionable.

Amounts of uranium in soil, water and food were measured in two areas in Russia (Berdinkova 1964). Uranium levels were also measured in the urine and feces of the residents (young individuals, age 2 to 3 years). Uranium was found in both the feces and the urine, indicating that some uranium was absorbed into the bloodstream. In the region with higher uranium in the water, total intake was calculated to be 0.3 mg uranium/day. Urine output was 3.2 µg uranium/day, and fecal excretion was 40 µg uranium/day. Data were not sufficient to determine the extent of uptake, since only about 10 percent of the intake could be accounted for.

2. Animals

Acute

In an experiment involving 27 elements, Hamilton (1948) administered uranyl nitrate-233 by gavage to rats at 0.3 mg uranium/kg and calculated absorption to be less than 0.05 percent. Of the initial absorbed dose, 45 percent went to the kidney and 20 percent to the bone. Recalculations by Durbin and Wrenn (1975), which involved summing the uranium contents of the tissues, provide an absorption value of 0.35 percent.

Rats were administered 0.51 µg (µCi) of uranium-233 or 9 µCi uranium-232 (as uranyl nitrate) by gavage (Sullivan 1980). Measurement of urine for 7 days and measurements of retention in skeleton and liver were used to calculate an absorption factor of 0.06 percent. Sullivan et al. (1983) administered 5.1, 12.6, or 25.3 mg uranium/kg as uranyl nitrate-233 by gavage to rats and then measured the amounts in the skeleton, liver and kidneys. They found that the percentage of gavaged dose which remained in these three tissues was 0.01, 0.0003 and 0.002, respectively. They calculated total absorption factors of 0.013, 0.013 and 0.02 for the three doses, indicating that mass had no effect on absorption. The data are from a table in an annual report, and no study details are provided. Wrenn et al. (1985) recalculated the absorption to be 0.044, 0.044 and 0.088 percent. In a later study, Sullivan et al. (1986) provided gavage doses of uranium-233 as uranyl nitrate to fed or fasted rats. One week later, uranium levels (as a percentage of the gavaged dose) in the tissues were determined. These percentages were found to be 0.0001 in the lung, 0.0004 in the liver, 0.002 in the kidney, 0.019 in the skeleton, and 0.045 in the urine, indicating that the total absorption was 0.067 percent. In fasted animals the absorption increased to 0.174 percent. In fasted animals treated with ferric iron, the absorption increased to 3.26 percent of the gavage dose. Sullivan and Ruemmler (1988) found that absorption of gavage doses of uranyl nitrate-233 was increased from 7.4 to 25.4 percent when the animals were fed an iron-deficient diet. These animals also had blood withdrawn to produce an anemic state (lowered hematocrit). Increased retention in liver, kidney and bone, as well as increased urinary excretion, were used as indicators of absorption.

LaTouche et al. (1987) administered 0.003 to 45 mg uranium/kg as uranyl nitrate-235 to 80 fasted Wistar rats. Uranium levels in blood, liver, kidney and bone were determined for up to 10 days. Cumulative urinary excretion was also measured, but was considered to be contaminated with fecal excretion. Gastrointestinal absorption was estimated by adding the kidney and skeletal burdens after 2 to 48 hours, and was calculated to be 0.6 to 2.8 percent. The highest value was associated with the highest gavage dose. The data presented a number of anomalies, so that the effects of mass on absorption could not be accurately determined. Experiments on fasted animals also showed that the fasted animals retained more uranium than the fed animals, indicating increased absorption.

Adult female Syrian hamsters were administered a gavage dose of 0.63 mg uranium/kg (Harrison and Stather 1981). They calculated an absorption of 0.77 percent for uranyl nitrate and 0.11 percent for uranium dioxide. The uranium was administered as 233-uranium dioxide in 0.1 M HNO_3, and the percent absorption was determined by comparing carcass and tissue uranium levels at 14 days with data obtained from intravenously dosed animals. In the same study, the absorption of a single oral dose of uranium dioxide (0.63 mg uranium/kg) by female hamsters was 0.11 percent.

An average absorption of 1.55 percent was obtained in a study with 10 dogs in which single doses of 0.7 mg uranium/kg (as UO_2F_2 enriched with uranium-233 and dissolved in water) were administered orally, and urine and feces were collected daily for 8 days post-dosing (Fish et al. 1960).

Larsen et al. (1984) estimated that absorption of orally administered uranium was 1.2 percent following administration of a single gavage dose of 0.53 μg uranium-233/kg (in a solution containing 0.01 M $NaHCO_3$) to one fasted adult baboon. The animal was simultaneously given an intravenous injection of 0.42 μg uranium-236/kg (also in a 0.01 M solution of $NaHCO_3$). The authors estimated absorption by comparing levels of the two radioisotopes in tissues and organs 32 days after dosing.

Uranium-233 (hexavalent) was administered by gavage, followed by uranium-236 intravenously, to four baboons fasted overnight (Bhattacharyya et al. 1989). Uranium levels were measured in blood 4 or 8 hours later. The animals were sacrificed 32 days after uranium administration, and uranium was measured in excreta and ashed tissues by both the direct analysis and dual isotope method. Two other baboons had the same treatment 2 hours after the morning feeding. Urine samples were collected for 4 days, and vertebrae samples were taken 14 days after uranium administration. Uranium levels were calculated by the dual isotope method. The authors calculated absorption by dividing output (urine and ashes) by input. The average absorption of four animals was 4.5 ± 2.8 percent. In animals that had eaten, the absorption was calculated to be 0.51 ± 0.006 percent. However, the fed animals had only a small tissue sample analyzed for uranium in the bone, so this cannot be directly compared to the data from the fasted baboons. The collection or measurement of uranium in the feces was not reported, and it is expected that this would contain a large amount of uranium. In another study, Bhattacharyya et al. (1989) administered uranium-233 by gavage and uranium-236 by intravenous injection to fed and fasted mice (10/group). The mice were sacrificed on day 6, and their whole bodies (without the head) were ashed. Details of uranium measurements were not provided. A table states that the mean percentage absorbed was 0.069 in the fed mice, and 0.80 in the fasted mice.

Chronic

Rats and rabbits were administered 1 to 600 mg uranyl nitrate/L in drinking water for 90 days, and results indicated that the uranium levels in kidney and bone increased with dosage. Using an estimate of 9.74 days as a retention coefficient, the uptake coefficient was calculated to be 0.035 percent in rats and 0.28 percent in rabbits (Tracy et al. 1983).

Haven and Hodge (1949) administered uranyl nitrate to rats in food for 30 days. Comparing the LD50 for dietary levels with the LD50 for intravenous injections, Wrenn et al. (1985) calculated the absorption factor to be 0.04 percent.

Maynard et al. (1953) administered uranyl fluoride or uranyl nitrate to rats in the diet for up to 2 years and measured uranium in bone ash. They calculated that 0.1 percent was absorbed from the gastrointestinal tract. Using estimates of 0.01/day for a turnover rate, and 0.2 for the fraction deposited in bone, Wrenn et al. (1985) calculated the absorption factor to be 0.038 to 0.078 percent.

Groups of 25 male and female rats were fed doses of 0, 0.1, 0.5, and 2.0 percent uranyl nitrate hexahydrate for 1 year (Maynard et al. 1953). The range for the uranium content of the kidneys in rats fed the 0.5 percent diet was 1.2 to 17 µg uranium/g, and for the rats fed 2 percent it was 1.3 to 82 µg uranium/g. It was calculated that rats on the 0.5 percent diet would have excreted 24 µg uranium/day. If these rats ate 10 g of diet, the intake would be 2500 µg uranium/day. Therefore, the authors estimated that the rats absorbed 0.1 percent of the uranium in the diet and deposited this amount in the skeleton.

B. DISTRIBUTION

Once ingested uranium is absorbed into the bloodstream from the gastrointestinal tract, it enters and leaves several compartments in the body. The most significant compartments are the blood, kidney and bone. Data are available from a limited number of human autopsy samples which show levels that are found in these organs. The intake of uranium in these people can also be approximated from estimated levels of uranium in food and drinking water. Since the number of subjects is small, and since the intake can only be estimated, there is uncertainty associated with attempting to relate levels in organs with levels of intake. Data are also available from animal studies. In these cases, the intake is well measured, and the relative distribution to the various organs can be more accurately estimated. This includes the fraction of organ uptake, as well as the biological half-life before elimination from the organ. The distribution of uranium within the kidney of animals has also been characterized, so that mechanisms of toxicity on the kidney can be proposed.

1. Blood

In eight samples of human blood from New York City residents, the concentration of uranium was determined to be 0.14 µg uranium/kg wet weight (Fisenne and Perry 1985).

Animal studies have revealed some of the details of the behavior of uranium within the blood. In general, there is an equilibrium between binding to bicarbonates and binding to protein. Cooper et al. (1982) administered uranyl nitrate-233 by intratracheal intubation to rats. They found that in blood, 50 percent of uranium is bound to transferrin, 25 percent to citrate and 25 percent to bicarbonate. Stevens et al. (1980) demonstrated that in dogs, 40 percent of the uranium in plasma complexes with protein and 60 percent complexes with bicarbonate.

Clearance of uranium from the blood occurs when the uranium is transported into extracellular fluid, deposited in bone, or filtered by the glomeruli of the kidney into the urine. The uranium which is complexed to bicarbonate is ultrafilterable and leaves the blood more readily than the fraction attached to the protein. Once this occurs, equilibrium is reached as the uranium which was attached to protein, sequestered in bone, returns to the plasma as the low molecular weight complex (primarily bicarbonate or citrate).

2. Kidney and Other Soft Tissues

From human autopsy cases in New York City residents, Fisenne and Welford (1986) measured uranium concentration in lung (28 samples), liver (28 samples), and kidney (9 samples). Samples were dry-ashed and uranium mass was measured fluorimetrically. The concentration in µg uranium per kg wet weight was 0.5 in lungs, 0.20 in liver, and 0.43 in kidneys. The material was separated by age groups, and although no distinctions were found with regard to concentrations in liver and kidney, age-related increases were found in concentrations in the lungs. No differences were found according to sex. Using Reference Man body weights, the authors estimate that the total burden was 0.5 µg in the lungs, 0.36 µg in the liver, and 0.13 µg in the kidneys. The mean concentration of uranium in the drinking water during a 10 year period was 0.03 to 0.08 µg/L.

Six patients were administered uranyl nitrate intravenously and two patients with terminal brain cancer were administered UCl_4 in an experiment in Boston. All patients were comatose and their physiology cannot be extrapolated to the general population. The patients survived 2 to 566 days post-injection. The retention in the kidney was 0.4 percent of the dose for the 566 day survivor and 16.6 percent for the 2 day survivor (Luessenhop et al. 1958, and Bernard and Struxness 1957 [as reported in Adams and Spoor 1974 and Hursh and Spoor 1973]).

Rats were administered 5.1, 12.6, or 25.3 mg uranium/kg as uranyl nitrate-233 by gavage; the amounts in the skeleton, liver and kidneys were measured one week later (Sullivan et al. 1983). They found that the percentage of gavaged dose which remained in these three tissues was 0.01, 0.0003 and 0.002, respectively. In another study, Sullivan et al. (1986) gavaged fed or fasted rats with uranium-233 as uranyl nitrate. One week later, uranium levels (calculated as a percentage of the gavaged dose) in the tissues were determined. These levels were found to be 0.0001 in the lung, 0.0004 in the liver, 0.002 in the kidney, 0.019 in the skeleton, and 0.045 in the urine. Levels were higher in fasted animals. Unfortunately, these data were not similar to those reported by Sullivan and Ruemmler (1988) who found that the percentage of gavage dose was 0 in the lung, 0.03 in the liver, 0.6 in the kidney, 2.1 in the skeleton, and 500 in the urine. LaTouche et al. (1987) administered uranyl nitrate by gavage to rats at doses of 0.003 to 45 mg uranium/kg. Fed animals had 11 ng/g in the kidney, and fasted animals had more (77 ng/g). Peak levels were reached 4 to 8 hours post gavage. Studies continued for 10 days post-gavage, but a steady state was not yet reached.

Rats were injected with a number of different elements; it was found that uranium levels in the kidney were 50 percent of the injected dose 1 day post-injection, 20 percent 4 days post-injection, and 0.2 percent 64 days post-injection Hamilton (1948). In the liver, less than 1 percent of the injected dose was found after 1 day, and this declined to less than 0.01 percent after 256 days. Bentley et al. (1985) injected female Wistar rats with natural uranium or uranium-235. Within 24 hours, the kidney contained 21 percent of the initial dose. This decreased to about 6 percent of the initial dose after 22 days.

Several parenteral studies from animals are available which provide data on the half-life of uranium in the kidney. All of these studies found that the elimination occurred in two phases. These were 2 and 50 to 60 days according to Diamond et al. (1989), 2 and 13 days according to Bentley et al. (1985), or 3 and 103 days according to Wrenn et al. (1986).

3. Distribution Within the Kidney and Elimination from the Kidney

In the renal glomerulus, the low-molecular weight uranium-bicarbonate or uranium-citrate complexes are filtered out of the bloodstream and passed into the proximal renal tubules (Voegtlin and Hodge 1949, 1953). Autoradiographies have shown uranium-232 which was injected intravenously 1 day prior to examination, deposited primarily in the proximal convoluted tubules, with lower concentration in the cortical medullary zone (Stevens et al. 1980). In these and other studies, uranium was not found in the glomeruli (Leggett 1989). However, other studies, using scanning electron microscopy, have shown that the glomerulus is adversely affected by uranium (Avasthi et al. 1980, Kobayashi et al. 1984).

In the proximal renal tubules, water and bicarbonate are absorbed, increasing the urine pH. As the pH of the glomerular filtrate decreases, the uranyl cations are liberated to combine with the phosphate ligands along the brush borders of the luminal surfaces of the cells in the tubular walls. This has been seen in autoradiographies of the kidneys of uranium-injected humans (Luessenhop et al. 1958). Recent studies have shown that it is possible that uranium enters the cytosol of the cells lining the tubules and then enters the lysosomes, mitochondria, or other organelles (see review by Leggett 1989).

The uranium in kidney equilibrates with uranium intake, so that at low levels of intake, kidney concentration of uranium is low. This is supported by findings that show that the uranium concentrations in kidneys of persons occupationally exposed is generally low (10 to 140 ng uranium/g wet tissue) and the uranium levels in unexposed persons are even lower (0.24 to 3.8 ng uranium/g wet tissue) (Hursh and Spoor 1973). There are at least two ways that uranium can leave the kidney: by complexing with natural ligands in tubular urine, or by being sloughed off with tubular cell debris. Dietary manipulations which lower urine pH impede uranium excretion, while alkalosis enhances it (Dounce 1949, Yuile 1973). At toxic uranium doses, the removal of uranium from the kidney is slowed by the damaged tubules.

4. Distribution to Bone and Teeth

The uranium concentration in thoracic vertebrae (40 samples) from human autopsy cases in New York City residents averaged 0.33 µg/kg wet weight (Fisenne and Welford 1986). The material was separated by age groups, and age-related increases were found in concentrations in the lungs and vertebrae. No differences were found according to sex. Using Reference Man body weights, the authors estimate that the total skeletal burden in these humans was 6.6 µg. The mean concentration of uranium in the drinking water during a 10 year period was 0.03 to 0.08 µg/L.

Luessenhop et al. (1958) and Bernard and Struxness (1957) (as reported in Adams and Spoor 1974, and Hursh and Spoor 1973) administered uranyl nitrate intravenously to six patients and UCl_4 to two patients with terminal brain cancer in an experiment in Boston. All patients were comatose and their physiology cannot be extrapolated to the general population. The patients survived 2 to 566 days post-injection. Retention in the bone was 1.3 percent of the initial dose for the man surviving 566 days, and 10 percent for the man surviving 2 days.

Welford and Baird (1967) found an average uranium concentration of 0.020 µg uranium/g in bone ash. The human material was first identified as being from New York, but was later found to have been from an area in the midwestern part of the United States known to have elevated levels of uranium in the drinking water (Fisenne and Welford 1986). Broadway and Strong (1983) found that the average concentration of uranium in human bones varied with age and with the type of isotope measured. Children less that 13 years old had higher levels than those aged 13 to 20 years. Uranium-234 and uranium-238 were more prevalent than uranium-235. For uranium-234, bone levels were 513 fCi/kg wet bone for the younger population, and 215 fCi/kg for the older one.

Forty-seven samples of rib and sternum were analyzed from Japanese subjects. An average concentration of 2.0 ng/g wet bone was reported (Nozaki et al. 1970). Belova and Lunkina (1967) measured uranium levels in food and water in two regions in Russia. The amount of uranium in human teeth was found to be higher in the region that had higher levels of uranium in the drinking water.

Male Wistar rats were given gavage doses of 0.003 to 45 mg uranium/kg of uranyl nitrate (LaTouche et al. 1987). Levels in the skeleton peaked at 4 to 8 hours post-gavage, and levels varied with dose. Animals were sacrificed for up to 10 days post-exposure, but the data do not indicate whether a steady-state had been reached by this time. At a treatment level of 0.3 mg uranium/kg, a 0.2 kg rat received 0.06 mg (60 µg) uranium. After 10 days, 0.14 µg was found in the skeleton, which was 0.2 percent of the administered dose. Data were similar for other treatment levels. In the femur, uranium concentration was 24 ng/g in fasted animals, and 8 ng/g in fed animals. Sullivan et al. (1983, 1986) administered 5.1, 12.6, or 25.3 mg uranium/kg as uranyl nitrate-233 by gavage to rats and found that 0.01 percent of the gavaged dose remained in the skeleton one week later.

Tracy et al. (1983) found that uranium levels in the bone of rats and rabbits increased with increasing doses of uranyl nitrate in the drinking water. Maynard et al. (1953) found that bone deposits increased from 12 to 16 µg uranium/g in rats fed the 2 percent diet of uranyl nitrate hexahydrate in the first week. At the end of the year, the deposits had increased to 200 µg uranium/g. The rats on the 0.5 percent diet reached a plateau representing a deposition of 16 to 18 µg uranium/g.

5. Distribution Within the Bone

The uranyl ion is associated with bone surfaces in close proximity to circulation: the trabeculae, endosteal and periosteal surfaces, and the vascular channels of cortical bone, as demonstrated by autoradiographies of rat femora (Tannenbaum and Silverstone 1951). These authors found that in adult dogs, uranium concentrations were 4 to 20 percent higher in trabecular bone than in compact bone.

Although uranium is initially deposited on the bone surface, it then can redistribute or diffuse into the bone volume. Both the surface and volume deposits can be quite heterogeneous. The redistribution pattern of uranium-233 from surface to volume is intermediate between that of plutonium-239, where most stays on the surface, and that of radium-226 where most goes to the bone volume (Stevens et al. 1980). Within the bone, the uranyl ion is bound to the surfaces of bone mineral crystals (Voegtlin and Hodge 1953).

The more vascular, immature skeleton presents a larger mineral surface that can take up uranyl ion more effectively than the more mature skeleton (Voegtlin and Hodge 1949). Immature rat skeletons showed an initial uptake of 15 to 25 percent of an injected dose, whereas mature skeletons only accumulated 11 to 12 percent of the dose. Not all the bones in the skeleton absorb or retain uranium equally. Thus, there is some error associated with predicting the content of the entire skeleton based on only a few bones (Singh et al. 1987).

6. Elimination from Bone

Uranium can be lost from bone by reverse ion exchange, and when bone structures are remodeled. Based on measurements made 8 months after a single uranium injection in rats, Hamilton (1948) calculated that the half-life of uranium in bone was 162 days. Leach et al. (1970) exposed monkeys and dogs to uranium in the air for up to 5 years. They calculated that the bone half-life was about 7 years.

Several models have been developed to describe the distribution and elimination of uranium from the bone and other organs. Adams and Spoor (1974) used data from Bernard and Struxness (1957) to derive equations for bone retention data which fit a least-square fitted power function or a two-term exponential function (the kidney data fit a simple power function and a two-term exponential function). Adams and Spoor (1974) also analyzed the data provided by Hursh and Spoor to fit bone and kidney retention curves to data from chronic exposures. Roswell and Wrenn (1980) modeled distribution and the consequences of that model were that 95 percent of the uranium going to the bone went to the compact bone (80 percent of skeletal mass) and had a half-life of 1 to 12 months. Only about 2 percent of the uranium was deposited in the spongy bone; however, it remained there longer, with a half-life of approximately 10 years.

C. EXCRETION

Data on excretion of uranium following oral intake are available from the same studies discussed above. The data are again limited by low numbers of subjects, but all the studies show that the vast majority of excretion is via the feces, and that a much smaller amount (about 1 percent) is excreted in the urine.

1. Human

Hursh et al. (1969) administered 10.8 mg uranium as uranyl nitrate (0.08 to 0.17 mg uranium/kg) orally to four men, and measured levels of radioactivity in the urine for 9 to 15 days. Uranium in feces was also measured for two men. The cumulative excretion for 9 days was 99.7 percent in one and 91.8 percent in the other. Since the second subject had one missing sample, the only reliable data is from one man who retained 0.3 percent of the administered dose for more than 9 days. This man excreted most (86 percent) of the administered dose in the feces within 2 days.

In a metabolic research unit, four men's uranium intake and excretion for 24 to 54 days was reported (Spencer et al. 1990). Urinary excretion was 1.8 percent of uranium-234 and 1.5 percent of uranium-238 intake. Fecal excretion was 74 and 75 percent for the two isotopes respectively. About 24 percent of the intake was unaccounted for, and may have remained in the body.

Masuda (1971a,b,c,d) measured urinary excretion in residents of three villages near a uranium mine in Japan. The urinary excretion ranged from nondetectable to 0.24 µg/day, as compared to nondetectable to 0.04 µg/day in a control village, with means of 0.15, 0.07 and 0.3 µg/day for the three exposed villages, and 0.006 µg/day for the control village. The dietary uranium intake was 3.9, 5.6, and 9.1 µg/day/person in the three villages, as compared to 1.8 in the control village. Levels of uranium in the water were not given, nor were levels of uranium in feces.

Uranium in feces and urine was measured in twelve subjects for 7 days (Singh et al. 1990, Singh and Wrenn 1987). The daily excretion was highly variable within and among subjects. The average daily excretion was 4.4 µg uranium/day in the urine. Data for fecal excretion was not completely presented. Average values, or values for all twelve subjects were not presented. Authors state that urinary excretion was 1 percent of total excretion. Drinking water samples were measured to have an average of 1.46 µg uranium/L.

Urinary and fecal excretion of uranium was measured in 19 mill crushermen exposed to uranium dioxide in the air (Fisher et al. 1983). The urinary excretion (about 6 disintegrations per minute (dpm)/day) was about 1 percent of fecal excretion (about 500 dpm/day).

Hursh and Spoor (1973) reported the results of Bassett et al. (1948) who performed experiments on humans given intravenous injections of uranyl nitrate. In these experiments in Rochester, six subjects received uranyl nitrate by the intravenous route, and 57 to 85 percent was excreted in the urine within 24 hours. Fecal excretion was minimal. Eight minutes after injection, only 11 percent of the administered dose remained in the blood. Hursh and Spoor (1973) also reported the data of Terepka et al. (1964) who measured 24-hour urinary excretions of 62 to 64 percent in three subjects, and Struxness et al. (1956) who measured 24-hour urinary excretions of 50 to 84 percent in six subjects.

2. Animal

Other than the data reported in the section on absorption, there are not adequate data regarding excretion of uranium in animals. One study did show that urine excretion of uranyl nitrate-233 increased in rats who were made anemic and placed on an iron-deficient diet (Sullivan and Ruemmler 1988).

D. BIOACCUMULATION AND RETENTION

The toxicokinetic model for uranium uptake and retention is derived from the ICRP model for uranium metabolism (ICRP 1979). The toxicokinetic model is based on human and animal studies of uranium administered intravenously or orally (ICRP 1979). The parameters used by EPA are given in Sullivan et al. (1981).

In general, retention is defined as the amount of a substance remaining in a tissue or organ at some time after the intake of the substance. The retention function R(t) specifies the fraction of a substance remaining in a tissue or organ at some time, t, after introduction. The retention function is frequently defined as a sum of terms of the form F x $\exp(-\lambda_B t)$ where each fraction, F, of a substance entering an organ or tissue has a corresponding biological removal rate coefficient, λ_B, or equivalently a biological half-life T_B. T_B and λ_B are related by the equation $\lambda_B = (\ln 2)/T_B$.

For a radionuclide with a radiological decay constant, λ_R, the retention function is modified by replacing each value of λ_B with the quantity $\lambda_E = \lambda_B + \lambda_R$.

Retention periods can be long for certain elements in some organs. Under those conditions, the organ burden of a long-lived radionuclide may include a significant fraction of all previous uptake of the radionuclide at that site. For continuous intake, this process of bioaccumulation can provide an organ burden which increases significantly over a persons's entire lifetime. The bioaccumulation is proportional to the convolution of intake rate and retention.

The numerical values for F and T_B are usually determined in studies where there is a known intake of a radionuclide. The whole body or specific organs or tissues are radioassayed to determine the amount of activity present at various times after intake. These data are used to develop a retention curve from which the numerical values of parameters can be obtained. Metabolic studies to determine retention parameters are usually done in experimental animals. However, for some radionuclides there are metabolic data from both humans and animals.

The EPA models differ from ICRP models in the treatment of radioactive daughters produced in the body (Dunning et al. 1984). ICRP assumes all radioactive progeny produced in the body follow the metabolic behavior of the parent nuclide (ICRP 1979). EPA permits each daughter, as it is formed, to assume the metabolic properties of that element.

Neptunium Model

The neptunium model is based primarily on animal studies and taken from the EPA model for transuranium elements (EPA 1977). The model parameters are:

1. Absorption from the intestine (f_1) is 0.001.
2. Fractional tissue uptake (f_2') is: bone, 0.45; liver, 0.45; testes, 0.00035; ovaries, 0.00011; other tissues, 0.07; excretion, 0.03.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	1.0	36525
Liver	1.0	14610
Testes	1.0	14610
Ovaries	1.0	14610
Other tissues	1.0	36525

Uranium Model

The toxicokinetic model for uranium is based on human and animal studies of uranium administered intravenously or orally (ICRP 1979). It is taken from the EPA models (Sullivan et al. 1981, Dunning et al. 1984, Begovich et al. 1981).

1. Absorption from the intestine (f_1) is 0.05 to 0.20.
2. Fractional tissue uptake (f_2') is: bone, 0.22; kidneys, 0.12; other tissues, 0.12; excretion, 0.54.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	0.9	20
	0.1	5000
Kidneys	0.996	6
	0.004	1500
Other tissues	0.996	6
	0.004	1500

Protoactinium Model

The protoactinium model is based on the models for transuranium elements developed by EPA for "Proposed Guidance for Transuranium Elements in the Environment" (EPA 1977). The model parameters are:

1. Absorption from the intestine (f_1) is 0.001.
2. Fractional tissue uptake (f_2') is: bone, 0.45; liver, 0.45; testes, 0.00035; ovaries, 0.00011; other tissues, 0.07; excretion, 0.03.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	1.0	36525
Liver	1.0	14610
Testes	1.0	14610
Ovaries	1.0	14610
Other tissues	1.0	36525

Thorium Model

Thorium uptake and retention has been studied in humans and animals. The thorium model is taken from ICRP 30 (ICRP 1979). The model parameters are:

1. Absorption from the intestine (f_1) is 2×10^{-4}.
2. Fractional tissue distribution (f_2') is: bone 0.70; liver, 0.04; other tissues, 0.16; excreta, 0.10.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	1.0	8000
Liver	1.0	700
Other tissues	1.0	700

Actinium Model

The actinium model is taken from Adams et al. (1978). The model parameters are:

1. Absorption from the intestine (f_1) is 0.001.
2. Fractional tissue distribution (f_2') is: bone 0.20; liver, 0.60; spleen, 0.05; other tissues, 0.15.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	1.0	3500
Liver	1.0	3500
Spleen	1.0	3500
Other tissues	1.0	3500

Radium Model

The radium model is based on human and animal studies of radium. The radium model is taken from Adams et al. (1978). The model parameters are:

1. Absorption from the intestine (f_1) is 0.20.
2. Fractional tissue uptake (f_2') is: bone, 0.46; other tissues, 0.54.
3. Radon retention in bone is 0.30.
4. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	0.525	0.023
	0.435	3.6
	0.022	1300
	0.00875	3500
	0.013	9600
Other tissues	0.16	0.05
	0.54	1.0
	0.11	35
	0.046	200
	0.009	1400

Francium Model

The current RADRISK toxicokinetic model for francium is taken from ICRP Publication 30 (ICRP 1981). The model parameters are:

1. Absorption from the intestine (f_1) is 1.0.
2. Fractional tissue uptake (f_2') is: all tissues, 1.0.
3. Retention parameters: Due to the short half-life of francium isotopes, francium is considered to transform in the organ in which it is deposited.

Radon Model

The radon model used by EPA is based on human and animal studies using radon and is generally supported by human and animal studies with inert gases (Bernard and Snyder 1975). The model parameters are:

1. Absorption from the intestine (f_1) is 1.0.
2. Fractional tissue uptake (f_2') is: all tissues, 1.0.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	0.70	2.65×10^{-4}
	0.30	∞
Other tissues	0.874	2.65×10^{-4}
	0.0913	0.0031
	0.0198	0.0288
	0.00863	0.146
	0.00612	0.963

Astatine Model

The current RADRISK toxicokinetic model for astatine is taken from ICRP Publication 30 (ICRP 1981). The model parameters are:

1. Absorption from the intestine (f_1) is 1.0.
2. Fractional tissue uptake (f_2') is: all tissues, 1.0.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
All tissues	1.0	10

Polonium Model

The polonium model is taken from ICRP 30 (ICRP 1979). The model parameters are:

1. Absorption from the intestine (f_1) is 0.10.
2. Fractional tissue uptake (f_2') is: liver, 0.10; kidney, 0.10; spleen, 0.10; other tissues, 0.70.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	1.0	50
Liver	1.0	50
Kidneys	1.0	50
Spleen	1.0	50
Other tissues	1.0	50

Bismuth Model

The bismuth model is taken from Adams et al. (1978). The model parameters are:

1. Absorption from the intestine (f_1) is 0.05.
2. Fractional tissue uptake (f_2') is: kidney, 0.40; other tissues, 0.60.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Kidneys	0.60	0.60
	0.40	5
Other tissues	0.60	0.60
	0.40	5

Lead Model

The lead model used is taken from Adams et al. (1978). The model parameters are:

1. Absorption from the intestine (f_1) is 0.20.
2. Fractional tissue distribution (f_2') is: bone 0.55; liver, 0.25; kidney, 0.02; other tissues 0.18.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Bone	0.60	12
	0.15	180
	0.25	12000
Liver	0.80	12
	0.18	180
	0.02	12000
Kidneys	0.80	12
	0.18	180
	0.02	12000
Other tissues	0.80	12
	0.18	180
	0.02	12000

Thallium Model

Thallium metabolism has been studied in humans and animals. The model is taken from Adams et al. (1978). The model parameters are:

1. Absorption from the intestine (f_1) is 0.95.
2. Fractional tissue distribution (f_2') is: kidneys, 0.05 and other tissues 0.95.
3. Retention parameters:

Organ	F (Fraction of organ burden)	T_B (Biological half-life in days)
Kidneys	1.0	7
Other tissues	1.0	7

The model listed above is used in an overall computer program, RADRISK, to calculate the concentration of uranium in body tissues (Dunning et al. 1980, Sullivan et al. 1981).

The activity in an organ at any time is calculated as:

$$\dot{A}_{ilk} = -(\lambda_i^R + \lambda_{ilk}^B)\ A_{ilk} + C_{ilk}\ (\lambda_i^R \textstyle\sum_{j=1}^{i-1} B_{ij} \sum_{r=1}^{L_{jk}} A_{jr} + p_{ik})\quad l = 1, \ldots\ldots, L_{ik}$$

where:

$\dot{A}_{ilk}$ = rate of change of activity of isotope i in compartment l organ k

L_{ik} = number of exponential terms in the retention function for isotope i in organ k

B_{ij} = branching ratio of nuclide to nuclide i

λ_i^R = rate coefficient (time^{-1}) for radiological decay of isotope i

λ_{ilk}^B = rate coefficient (time^{-1}) for biological removal of isotope i, from compartment l of organ k

C_{ilk} = fractional coefficient for nuclide i in the ith compartment of organ k

p_{ik} = inflow rate of isotope i into organ k

The function is evaluated for a constant inflow rate per year, 1 pCi/year in most cases.

Retention is calculated in a similar manner (Sullivan et al. 1981):

$$R_{ik}(t) = \textstyle\sum_{l=1}^{L_{ik}} C_{ilk} \exp[-(\lambda_i^R + \lambda_{ilk}^B)t]$$

where:

$R_{ik}(t)$ = retention of isotope i at time t after intake, in organ k.

Concentration of activity or integrated activity in an organ or tissue can be calculated using these computer programs. Computed values are stored in a file and later passed to another program which calculates dose and dose rate from the activity concentrations. Dosimetric estimates calculated in this way are used with age specific risk coefficients to calculate the risk from a specified radionuclide intake. Further information on these calculations can be found in Sections VII and VIII.

V. HEALTH EFFECTS IN ANIMALS

Animals were exposed to uranium and its compounds by the oral, parenteral, and inhalation routes in both short- and long-term experiments. The studies show that uranium is primarily a kidney toxicant, affecting the renal proximal convoluted tubules. The older studies, which focused on high doses, found that uranium caused increased mortality and that the toxicity of the uranium compounds varied, with uranyl fluoride being the most toxic. Limited studies are available on the carcinogenicity of uranium in animals; there is one study using the inhalation route of exposure, and one using intraperitoneal injection.

A. SHORT-TERM EXPOSURE (less than 90 days)

1. Oral Studies

Rats and mice were administered gavage doses and subcutaneous injections of uranyl acetate (Domingo et al. 1987). The oral LD_{50} for rats was calculated to be 204 mg/kg, and for mice it was 242 mg/kg. These were much higher than the subcutaneous LD_{50}s (8.3 mg/kg for rats and 20.4 mg/kg for mice) indicating a low gastrointestinal absorption rate. Food intake decreased, as did body weight. Urine excretion increased significantly (but drinking levels did not) as did protein and creatinine levels in the urine, indicating a disorder in renal function. Minimal microscopic lesions were found in the liver and kidney. More severe lesions were found following the subcutaneous doses.

Goel et al. (1980) provided 20 mg of uranyl nitrate in the food on alternate days to rats which were sacrificed after 15, 19 or 27 days. Food consumption not reported, nor was the number of days they were exposed to uranyl nitrate in the food, so dose cannot be accurately determined. Glomerular and tubular histopathology were noted, consisting of increased space between glomerular capsule wall and the glomerulus, and hydropic degeneration of proximal tubular epithelium. Other results of this study (Goel et al. 1979) reveal necrosis, pycnotic nuclei and infiltration of cells in the centrilobular and perilobular regions of the liver.

Rats were administered uranyl acetate in the drinking water for 4 weeks at levels of 0, 2, 4, 8, or 16 mg/kg/day (Ortega et al. 1989). No significant effects were seen on food intake, water intake, weight gain, or urinary measurements of total protein, urea or creatinine. No changes were seen in organ weights, including kidney. At the highest dose, a moderate increase in lysosomal content of the epithelial cells of the proximal convoluted tubule was noted, but the rest of the nephron was normal. Hematological changes were seen at the highest dose. These included very slight increases in hematocrit, erythrocytes, and hemoglobin. The plasma had an increase in glucose, total protein, GOT and GPT.

Groups of male and female rats (strain not reported) were administered nine uranium compounds in the diet at widely divergent doses for 30 days (Maynard and Hodge 1949). Rats were observed daily for clinical signs of toxicity, and body weights were recorded weekly. At termination, necropsies were performed, organ weights were determined, and the heart, lung, stomach, small and large intestines, liver, spleen, and kidneys underwent histopathological examination. Of the nine compounds tested, three compounds were nontoxic: uranium dioxide (UO_2), uranium tritaoctoxide (U_3O_8), and uranium tetrafluoride (UF4). Uranium dioxide and uranium tritaoctoxide, when administered at dietary levels of 220, 881, or 8,810 mg uranium dioxide/kg/day or 212, 848, or 8,480 mg uranium tritaoctoxide/kg/day, produced no body weight depressions and caused no deaths. However, at a level of 7,570 mg uranium/kg/day, uranium tetrafluoride caused death in one female and produced marked loss of growth in both sexes, while lower levels of this compound produced no effects.

The remaining six compounds were toxic. At dietary levels of 2 to 20 percent, these compounds caused 100 percent mortality; at levels of 0.1 to 1.0 percent, they produced growth depressions. Treatment-related histopathological changes were observed in the kidneys of rats fed the toxic uranium compounds (UO_2F_2, $UO_2(NO_3)_2 6H_2O$, UCl_4, UO_3, UO_4, and UO_2Ac_2). Evidence of active epithelial damage was seen in rats that died following 2 weeks of treatment. Rats surviving the 30-day treatment period exhibited a predominance of regenerative processes in the kidneys. The degree and frequency of renal changes varied considerably depending on the dose and compound. No histopathological changes were observed in rats fed the insoluble nontoxic uranium compounds (UO_2, UF_4, and U_3O_8). In another experiment, weanling and adult rats (6 months old) were fed 237 mg uranyl nitrate/kg/day for 1 month. Mature rats were more susceptible to uranium toxicity than weanling rats. Mortality rate was 12 and 21 percent in male and female weanling rats, respectively. The corresponding values in adult rats were 76 and 68 percent. Although both age groups lost weight during the first week, the weanlings gained weight rapidly and the adult rats gained weight at a much slower pace. In general, no significant changes were observed in the hematological parameters in any of the treatment groups. However, small decreases in the red blood cell count, hemoglobin, and reticulocyte percentages were observed in adult rats fed uranyl nitrate hexahydrate. The biological significance of this finding was not known.

Young beagle dogs (number/group and sex not specified) were administered 11 uranium compounds either mixed in their diet or via capsules (due to unpalatability) for 30 days (Maynard and Hodge 1949). The presence or absence of toxicity was based on the criteria of mortality, blood NPN, urea nitrogen, and histopathological changes in the kidneys, liver, and gastrointestinal tract. The urinary volume followed a course of polyuria succeeded by oliguria. Four days after administration of 0.5 g uranyl nitrate hexahydrate, non-protein nitrogen and urea nitrogen increased. High levels of urinary sugar and protein were found in the most severely ill animals who died before termination of the experiment.

Groups of six rabbits (strain and sex not reported) were administered uranyl nitrate hexahydrate at 0, 2.84, 14.2, or 70.95 mg/kg/day (0, 0.02, 0.1, or 0.5 percent) in the diet for 30 days (Maynard and Hodge 1949). Animals were examined daily, body weights were recorded weekly, and kidneys were examined histologically. All six rabbits fed the 0.5 percent diet died by study day 12, and three rabbits fed the 0.1 percent diet died by study day 23; no rabbits died at the 0.02 percent level. Body weight losses were observed at all three levels but were minimal in rabbits fed the low dose (0.02 percent). Necropsy revealed no gross abnormalities. Histopathology revealed renal damage at all levels; the effect was moderately severe at the 0.5 percent level and moderate at 0.02 and 0.1 percent.

2. Inhalation Studies

Groups of 16 female beagle dogs were exposed to aerosol concentrations of 100 to 500 mg uranyl fluoride/m^3 for periods ranging from 30 minutes to about 2.5 hours (Morrow et al. 1982). After 1 to 3 days of exposure, scattered necrosis was seen in the convoluted tubules of the kidneys, along with hyaline material and casts. Glomerular capillaries were congested. Tubular regeneration was seen after 6 days.

In 46 short-term inhalation studies (Dygert et al. 1949), mice, rats, hamsters, guinea pigs, rabbits, cats, and dogs were exposed to 12 uranium dusts: uranium hexafluoride (UF_6); uranyl fluoride (UO_2F_2); uranyl nitrate ($UO_2(NO_3)_2 6H_2O$); uranium tetrachloride (UCl_4); uranium tetrafluoride (UF_4); uranium dioxide (UO_2); uranium trioxide (UO_3); uranium peroxide (UO_4); sodium diuranate ($Na_2U_2O_7$); ammonium diuranate $(NH_4)_2U_2O_7$; uranium tritaoctoxide (U_3O_8); and high-grade uranium ore. Criteria of toxicity were used to define the acute responses to the uranium dusts: mortality, body weight loss, increased levels of blood NPN and blood sugar, histopathological changes (notably in the kidneys, liver, and lung), changes in hematological parameters, and in most studies, uranium content in the tissues. As in the dietary studies, the water-soluble UF_6, UO_2F_2, UCl_4, and uranyl nitrate compounds were the most toxic. The less soluble salts (UO_2, UF_4) and the high-grade ore were occasionally fatal to some species and induced mostly moderate to severe renal damage at high concentrations. The peroxide and diuranates of ammonium and sodium had an intermediate effect; U_3O_8 was almost without effect. Because of the route of exposure (inhalation), these studies have limited relevance to ingestion of uranium.

3. Intravenous Studies

The acute effects of uranyl nitrate, uranyl fluoride, and uranium tetrachloride were reported following parenteral administration to mice, rats, guinea pigs, or rabbits (Haven and Hodge 1949). Rats showed a significant increase in toxicity with increasing age. Uranyl fluoride was more toxic than uranyl nitrate or uranium tetrachloride. The increase in toxicity from compound to compound had a high degree of regularity whether measured in young or old rats. Mortality patterns observed at 14 to 21 days showed a difference between sexes: males were more resistant than females. Prior to death, clinical signs of toxicity, which were similar for all three compounds, included the following: diarrhea, red crust around the nose, lethargy, convulsions, coma, and blood in the abdominal cavity. In rats treated with uranyl nitrate and uranyl fluoride, hemorrhages were found in the walls of the small intestine. In rats treated with uranyl fluoride, the livers and spleen frequently appeared gray.

Diamond et al. (1989) administered uranyl fluoride (0.66 or 1.32 mg uranium/kg) intravenously to rats. Renal injury, characterized by cellular and tubular necrosis of the distal portions of the proximal tubule, loss of PAS-staining in proximal tubule brush borders, and tubular cell apoptosis, was evident at uranium levels of 0.7 to 1.4 µg/g wet kidney. Renal function abnormalities included impaired tubular reabsorption, proteinuria and enzymuria. Repair was rapid, with restoration of histology 35 days post exposure.

The influence of age on acute renal toxicity of uranyl nitrate was studied in young (aged 1 to 2 weeks) and old (aged 3 to 5 weeks) male and female mongrel puppies (Pelayo et al. 1983). Renal function and morphologic studies were conducted 2 hours (initiation phase) and 24 hours (maintenance phase) following intravenous administration of 10 mg uranyl nitrate/kg (4.7 mg uranium/kg). Age-matched controls received the vehicle only. In the young puppies (1 to 2 weeks), treatment produced no changes in the whole-kidney glomerular filtration rate (GFR) despite a significant ($p < 0.01$) reduction in renal plasma flow (RPF). In contrast, during the maintenance phase (24 hours), GFR was lower (60 percent) in treated dogs as compared with controls ($p < 0.02$), while the values for RPF were nearly identical to control values. In the older puppies (3 to 5 weeks), GFR was completely suppressed ($p < 0.001$) during the maintenance phase, and RPF values were similar to control values. The age-related morphologic alterations observed in the proximal tubules of the most differentiated nephrons correlated well with the functional responses. A greater proportion of functional and morphologic alterations was observed in the older dogs; younger animals were much less affected.

Female Wistar rats were injected with natural uranium or uranium-235 (Bentley et al. 1985). At the 500 µg/kg dose, the proximal convoluted tubules showed necrosis with much hyaline material and cellular debris. Tubular regeneration was apparent 5 to 6 days post-exposure. After 12 days, regeneration appeared complete. Transient disturbances in urinary protein, nitrogen base and amino acid excretion were noted. Urinary creatinine excretion was only marginally depressed. Non-protein nitrogen retention was increased.

Bowman and Foulkes (1970) injected 0.2 mg uranium/kg as uranyl acetate intravenously into rabbits. Both the proximal and distal convoluted tubules were adversely affected, as well as Henle's loop, as indicated by increased sodium and water excretion. Potassium excretion was not affected. Kobayashi et al. (1984) intravenously injected rabbits 2 mg uranyl acetate/kg. They found decreased creatinine clearance, and by 5 days, urine flow was reduced to almost zero. Scanning electron micrographs revealed a spreading of epithelial podocyte cell bodies, and a reduction in endothelial fenestrae in the glomerulus. These alterations were not seen 14 days post-injection, and glomerular function also returned to normal.

Kidney toxicity was found in rats given intravenous injections of 15 or 25 mg uranyl nitrate/kg (Avasthi et al. 1980). Electron micrographs revealed a slight reduction in glomerular endothelial fenestral density, and a more dramatic decrease in fenestral diameters. This could result in the reduction of the ultrafiltration coefficient of glomerular capillaries, leading to acute renal failure. Creatinine clearance, sodium excretion, and urine osmolarity were also decreased. Sodium-loaded rats failed to develop the functional or morphological alterations.

4. Subcutaneous Studies

Groups of 26 Sprague-Dawley rats were given a single subcutaneous injection of 14.4 mg uranyl nitrate hexahydrate/kg in saline solution (Stone et al. 1961). The rats were sacrificed after 18, 24, and 36 hours, and 2, 3, 4, 5, and 6 days. The significant treatment-related changes observed in the kidneys were necrosis, enlargement of subbasilar compartments, and an increase in and enlargement of cytoplasmic vacuoles and bodies. Necrosis increased gradually and became severe on day 4 when the tubules were filled with debris. The subbasilar compartments of the proximal, distal, and collecting tubules became considerably enlarged on day 1 and decreased in size and frequency thereafter. These changes were maximal at the time of polyuria and were thought to be apparently related to fluid transport. Large cytoplasmic vacuoles and bodies were prominent on day 3 and were probably due to tubular resorption. Kidney tubules (proximal, distal, and collecting) of untreated and saline-injected rats were similar and were comparable to those seen in normal animals.

Haley (1982) injected male Sprague-Dawley rats subcutaneously with 10 mg uranyl nitrate/kg (4.7 mg uranium/kg). Morphological changes observed in the kidneys as early as 1 hour post-injection became progressively severe during the next 5 days. Disruptions included a loss of microvilli in the brush border and increased vacuolization in the proximal convoluted tubules, continuing to complete necrosis. Casts were formed in the loop of Henle. Scanning electron microscopy revealed flattened and swelled podocytes in glomerular epithelial cells. In further studies, Haley (1982) found that glomerular filtration rate was significantly reduced and that sodium excretion increased. This dose was very near the maximum-tolerated level, for there was a 60 percent mortality rate. Two weeks post injection, the tubular epithelial lining was beginning to repair itself; however, the tubules remained dilated and the cells were flatter than normal. Interstitial fibrosis remained for the one week observation period.

Uranium dioxide particles at 0.01, 0.05, 0.5, or 1.0 g/kg were subcutaneously implanted into the dorsal skin of 10 female Wistar rats (De Rey et al. 1984). The animals were sacrificed at 3, 6, 24, and 48 hours after implantation. Light and electron microscopic examination revealed increasing stages of proximal tubular epithelial necrosis of the kidneys. Acute renal failure caused death within 6 days in rats implanted with doses >0.01 g uranium dioxide/kg.

B. LONG-TERM EXPOSURE

Extensive studies were conducted by Maynard and Hodge (1949) using albino rats exposed for 1 year via the diet. Uranyl fluoride was administered at 0, 0.01, 0.05, 0.10, 0.15, 0.25, 0.50, or 0.75 percent to groups of 15 to 25 rats of either sex. Uranyl nitrate was administered at 0, 0.01, 0.05, 0.1, 0.5, 1.0, or 2 percent to groups of 15 to 25 rats of either sex. Both uranyl tetrafluoride and uranium dioxide were administered at 0, 0.5, 2.0, or 20 percent to groups of 15 male and 15 female rats. Uranium dioxide showed no evidence of toxicity. No treatment-related mortality, body weight depression, or histopathological changes were observed up to the 20 percent diet.

Uranyl tetrafluoride was the least toxic, even at high doses. Mortality occurred in 4 percent of treated males and in 20 percent of females; the corresponding figures for the controls were 12 and 9 percent, respectively. The reason for the high mortality among the females is not known. Rats fed the 0.5 or 2 percent diet consistently outweighed the controls. The only treatment-related effect seen throughout the study was a marked depression in the body weights of males and females fed the 20 percent diet.

Uranyl nitrate was moderately toxic at medium doses. Mortality among the treated rats (16 percent males and 11 percent females) was comparable to that of the controls (12 percent males and 9 percent females). Growth rates were consistently lower in rats fed the $\geq$0.5 percent diets, with the effect being severe at the 1 and 2 percent levels. Body weights of rats at the lower levels (0.01, 0.05, and 0.1 percent) were similar to those of the controls. Hematological studies showed a decrease in the RBC counts and hemoglobin values (low-grade anemia) in both sexes of rats and some evidence of an increase in WBC counts, absolute neutrophils, and absolute lymphocytes (low-grade leukocytosis) in the females fed the 2 percent diet. Histopathological examination revealed no treatment-related pathological changes in rats fed the 0.1 percent diet. At the 0.5 percent level, a transient slight injury occurred in the kidney, with nearly complete recovery. Rats maintained on the 2 percent diet showed moderately severe necrosis initially, followed by regeneration. In addition, progressive atrophic changes were observed in the tubules of kidneys along with an increase in stroma and narrowing of the cortex. Male rats sacrificed at 52 weeks showed changes in the seminiferous tubules of the testes. Although these changes were not observed in the control rats and were limited to only the 2 percent diet group, it was not apparent to the investigators that these changes were due to a direct action of uranium. No significant histopathological changes were observed in the other tissues.

Uranyl fluoride was more toxic, even at low doses. Mortality occurred in 100 percent of rats fed the 0.75 percent diet by the end of 2 months of treatment, and in 57 percent of the males and 33 percent of the females fed the 0.50 percent diet by the end of 12 months. Mortality among rats fed the lower levels (0.01 to 0.25 percent) was comparable to that of the controls. Unequivocal evidence of growth depression was observed in males fed the ≥0.1 percent diets; treated rats consistently weighed less than the controls throughout the 12-month period. However, the dose levels (0.1, 0.15, and 0.25 percent) that caused a body weight depression did not have an adverse effect on mortality. Body weights of rats at the lower dose levels (0.01 and 0.05 percent) were similar to those of the control rats. At 0.15 percent (60 mg/kg/day) of uranyl fluoride in the diet, renal changes were minimal. Marked tubular atrophy with later regeneration was seen at the highest dose. Urine contained normal glucose and protein levels.

Groups of 15 to 25 male and female rats surviving the 1-year treatment with the four uranium compounds were continued on their respective diets for a second year (Maynard and Hodge 1949, Maynard et al. 1953). The treatment regimens were as follows: uranyl fluoride at 0, 0.01, 0.05, 0.10, 0.15, 0.25, or 0.50 percent; uranyl nitrate at 0, 0.01, 0.05, 0.1, 0.5, 1.0, or 2.0 percent; and uranium tetrafluoride or uranium dioxide each at 0, 0.5, 2.0, or 20 percent. Hematological studies including red blood cell counts, hemoglobin values, white blood cell counts, and differential counts were conducted at monthly intervals. Pooled urine samples collected at monthly intervals were analyzed for sugar and protein. Samples of kidneys and femurs taken from a number of rats were analyzed for uranium content. At termination, gross necropsy was performed and all major organs underwent histopathological examination. In general, there was no evidence of increased mortality with continuation of the treatment. The lifespan of the animals was not affected at dietary levels as high as 0.05 percent uranyl fluoride, 2 percent uranyl nitrate, or 20 percent uranyl tetrafluoride, or uranium dioxide. Body weight depressions observed at various dietary levels were as follows: slight change at 0.1 percent uranyl fluoride and large change at 0.15 percent uranyl fluoride, 0.5 percent uranyl nitrate, and 20 percent uranyl tetrafluoride; no body weight depression was seen at any level of uranium dioxide. No treatment-related changes in the hematological parameters were observed in rats fed uranium tetrafluoride or uranium dioxide, or in males fed uranyl nitrate. Rats fed 0.25 or 0.5 percent uranyl fluoride showed a trend toward lower red blood cell counts and hemoglobin values, and toward higher white blood cell counts and neutrophil values, as compared with controls. Females fed 1 or 2 percent uranyl nitrate showed a tendency toward anemia and a low-grade increase in white blood cell counts.

Thirty dogs were fed various daily doses of five uranium compounds (uranyl fluoride, uranium tetrachloride, uranyl nitrate, uranium dioxide, and uranium tetrafluoride) for a period of 1 year (Maynard and Hodge 1949, Maynard et al. 1953). The dose levels were selected based on a 30-day study, and the dogs received the uranium compounds at levels that were tolerated for 1 year. The dose levels were as follows: 0.2, 1, 0.005, 10, or 25 mg uranyl fluoride/kg/day; 2, 10, or 50 mg uranium tetrachloride/kg/day; 20, 100, or 200 mg uranyl nitrate/kg/day, 1, 5, or 10 g uranium dioxide/kg/day; or 0.2, 1, or 5 g uranium tetrafluoride/kg/day. A total of 16 dogs served as the untreated control group. Dogs were observed daily for clinical signs of toxicity, and blood samples taken weekly during the first months were screened for blood NPN, urea nitrogen, serum protein, and hematological parameters. Urine samples collected weekly were examined for sugar, protein, pH, and specific gravity. At termination, histopathological examinations of all the major organs were conducted. At termination, severe body weight losses were observed in the two dogs fed 200 mg uranyl nitrate/kg/day; one of these dogs died after 138 days of treatment. No significant effects on body weight were observed in dogs fed the lower levels of uranyl nitrate or in those fed other uranium compounds. No marked abnormalities were observed in the hematological parameters (RBC, WBC, hemoglobin, and differential counts) measured at various intervals. Except for the two dogs fed 200 mg uranyl nitrate/kg/day, there were no extreme elevations of blood NPN or urea nitrogen; no signs of acute uranium poisoning were seen in most of the studies. Some scattered abnormal urinary protein and sugar values were observed. These were noticeable in one dog fed 50 mg uranium tetrachloride/kg/day and in one dog fed 200 mg uranyl nitrate/kg/day. The principal pathological finding consisted of the renal-cortical tubular changes in the dogs fed all five uranium compounds. The minimum dietary levels that produced pathological changes in the kidneys were as follows: 25 mg uranyl fluoride/kg/day, 50 mg uranyl tetrachloride/kg/day, 20 mg uranyl nitrate/kg/day, 1 mg uranium dioxide/kg/day, and 0.2 mg uranium tetrafluoride/kg/day. This study is of limited value for establishing a NOAEL or LOAEL because only two dogs per group were used. This limited number is not acceptable by current standards for a chronic study in dogs.

Tannenbaum and Silverstone (1951) administered uranium dioxide (1,000 mg uranium/kg), uranium tetrafluoride (5,000 mg uranium/kg) and uranyl nitrate (400 mg uranium/kg) in the diet of mice for 48 weeks. No pathologic changes in the kidneys were found, except for necrosis in mice receiving 800 mg uranyl nitrate/kg.

C. REPRODUCTIVE/DEVELOPMENTAL

Paternain et al. (1989) studied the effects of uranium on reproduction, gestation, and postnatal survival in Swiss mice. Groups of 25 male mice were orally administered, by gavage, uranyl acetate dihydrate at 0, 5, 10, or 25 mg/kg/day for 60 days prior to mating with female mice (25/group) that had received the same oral doses of the compound for 14 days prior to mating. Treatment of the females continued throughout mating, gestation, parturition, and nursing of the pups. Half the dams in each group were sacrificed on day 13 of gestation, and the remaining dams were allowed to deliver and wean their offspring. Postnatal development was monitored after 0, 4, and 21 days of lactation. Uranyl acetate induced embryolethality and had an adverse effect on fetal and neonatal development at the 25 mg/kg/day level. At this level, a significant ($p < 0.05$) increase was noted in the number of resorptions and in the number of dead young/litter at birth and at day 4 of lactation. In addition, fetal body weights and lengths were significantly ($p < 0.05$) lower on days 0, 4, and 21 at the high dose. Significant ($p < 0.05$) differences in fetal body weights were also observed in the 10 mg/kg/day group on days 4 and 21, and in the 5 mg/kg/day group on day 21.

The developmental toxicity of uranium was evaluated in groups of 20 Swiss mice orally administered uranyl acetate dihydrate, by gavage, at 0, 5, 10, 25 or 50 mg/kg on gestation days 6 through 15 (Domingo et al. 1989a). Dams were sacrificed on gestation day 18, and fetuses were examined for external, visceral, and skeletal abnormalities. Treatment caused maternal toxicity as manifested by significant ($p < 0.05$), dose-related reductions in body weight gain during dosing; significant ($p < 0.01$) reductions in food consumption in the 10, 25, or 50 mg/kg/day groups; and a significant ($p < 0.05$), dose-related increase in maternal liver weights. Maternal kidney weights were significantly ($p < 0.05$) increased only at the highest dose. No treatment-related effects were observed for the number of implantation sites/dam, or on the incidence of post-implantation loss (resorptions plus dead fetuses). The number of live fetuses/litter and the fetal sex ratio were not affected by the treatment. However, treatment did cause significant ($p < 0.05$) dose-related fetal toxicity consisting primarily of reduced fetal body weight and length, increased number of stunted fetuses/litter, and increased incidence of abnormalities. Malformations (cleft palate, bipartite sternebrae) and developmental variations (reduced ossification and unossified skeletal variations) were observed at the 25- and 50-mg/kg/day levels. The NOAEL for maternal fetal toxicity was below 5 mg/kg/day; the NOAEL for fetotoxicity was also below 5 mg/kg/day, as some anomalies were observed at this dose. It is important to note that effects were noted in the lowest non-zero dose group. In a related study (Domingo et al. 1989b), mice were administered uranium orally. Dams were given 0.5 mg/kg/day of uranyl acetate and the brain weight in the weaning mice was increased with statistical significance. An intake rate of 0.05 mg/kg/day of uranyl acetate produced decreased liver weight.

In a breeding study, groups of 50 male and 50 female rats, in pairs, were fed 2 percent uranyl nitrate hexahydrate in the diet for 7 months followed by a regular stock laboratory diet for an additional 5 months (Maynard and Hodge 1949). An equal number of rats of each sex were given the stock laboratory diet for 1 year. Rats were allowed to mate, the litters were removed at birth, and the females were mated again. Body weights of treated rats of both sexes were noticeably depressed when compared with the respective controls. Uranyl nitrate produced some interference with normal reproduction. Treated females had fewer litters (135 litters in treated females versus 249 in controls). The frequency of litters was slightly reduced in treated rats (an average frequency of 18 in treated versus 33.7 in controls), and the average number of pups/litter was reduced (an average of 7.96 offspring in treated versus 9.12 in controls). The estrous cycles were irregular in treated females that had no matings during the fourth, fifth, and sixth months; 13 of 17 treated versus two of four controls had irregular estrous cycles. When the treated rats were shifted to the stock laboratory diet for 5 months, the growth rate promptly resumed with the body weights of treated rats almost reaching those of the control rats at termination. An increased birth rate was also indicated. During this period, the controls had 104 litters and the treated groups had 72 litters. Despite cessation of treatment, failure to produce litters continued among the treated females that had failed to produce litters during the treatment period. The authors postulated that a reduction in food intake may have caused the depressed growth and may have interfered with normal reproduction. Thus, the loss of fertility might be attributed to malnutrition, to the effects of uranium in the diet, or to both.

A follow-up study (Maynard et al. 1953) was conducted to examine whether uranium administration might influence reproduction in the absence of a body weight loss. Groups of 50 male and 50 female rats, in pairs, were fed either a stock laboratory diet or a 2 percent uranyl nitrate hexahydrate diet for a single 24-hour period and were then fed the stock diet for 9 months. Animals were allowed to mate, litters were removed at birth, and the rats were re-mated. The growth rates of treated and control rats of both sexes were identical. The interference of malnutrition in the reproductive function is presumably absent in this study. Treated rats had fewer litters (a decrease of 7 percent), fewer pups per litter (a decrease of 0.7), and a lower number of offspring (a decrease of 12 percent). The authors concluded that in the absence of any serious interference with nutrition, a single dose of 2 percent uranyl nitrate adversely affected the reproductive function of rats.

Groups of 25 male and female rats were placed on diets containing 0, 0.1, 0.5, and 2 percent uranyl nitrate hexahydrate for one year. During the first month all rats showed histological evidence of immaturity in the testes. After one year, all rats that had received the 2 percent dose showed evidence of testicular abnormalities. The proximal ducts of the epididymis and vas deferens showed moderate to complete depletion of spermatozoa (Maynard et al. 1953).

Jadon and Mathur (1983) gave groups of seven male Swiss mice daily intraperitoneal injections of an aqueous solution of uranyl nitrate at 0 or 0.05 mM/100 g body weight for 7 days and sacrificed the animals 24 hours after the last treatment. Histologic and cytometric studies of the testes were conducted. Histopathology revealed deformation of the seminiferous tubules with conspicuous vacuoles and extensive degeneration of spermatogenesis, mononucleate and polynucleate giant cells, and exfoliated germ cells in most of the tubules. When compared with the vehicle control, treatment decreased testes weights and caused significant reductions in the diameter of the seminiferous tubules ($p < 0.01$) and in the number of Leydig cells ($p < 0.001$). Significant ($p < 0.001$) reductions in the gametogenic counts (spg., R-sp-cyt, pachytene spermatocytes, and Stage VII spermatids) were observed in treated animals.

D. MUTAGENICITY

No data were located regarding the mutagenic effects of uranium in animals. However, there is a substantial body of literature showing the effects of radiation in animal genotoxicity tests with other radioisotopes.

E. CARCINOGENICITY

No carcinogenicity studies of uranium compounds administered via the oral route were available in the literature.

In a chronic inhalation study, 95 female Wistar rats, 38 male and 72 female beagle dogs, and 20 female rhesus monkeys were exposed to natural uranium as uranium dioxide at 5 mg/m^3 (MMD = 1 μm), 6 hours/day, 5 days/week for 1 to 5 years. Of the 13 dogs that survived up to 75 months post-exposure, two developed adenomas without malignancy and two developed glandular neoplasms that invaded the adjacent area. The authors stated that the neoplasms observed in dogs should not be used to extrapolate carcinogenicity in humans because very few animals were affected, and these types of neoplasms (glandular) are rare in cases of human lung cancer (squamous cell carcinomas are frequently seen in humans) and are thought to be caused by environmental factors. No tumors were observed in rats or monkeys (Leach et al. 1970, 1973).

Finkel (1953) examined the long-term radiation effects of intravenously injected alpha-emitting, bone-seeking radionuclides including uranium-232, uranium-233, U_{nat}, and radon-226 in female CF_1 mice. At the high dose, both nuclides reduced the lifespan of mice. Malignant bone tumors were observed in mice injected with uranium-232 and uranium-233. In mice injected with uranium-232 (0.1, 1, or 10 µCi/kg), malignant bone tumor incidences were 3, 11, and 60 percent. Following injection of uranium-233 (0.1 to 100 µCi/kg), the tumor incidences were 8 to 22 percent in mice injected with <25 µCi/kg of the isotope. Injection of U_{nat} (6.8×10^{-6} to 6.8×10^{-4} µCi/kg) was not associated with malignant bone tumors. The incidence of bone tumors was 0.8 percent in a control group consisting of 120 animals. This was to be expected given the low doses from this low specific activity uranium.

F. SUMMARY

Toxicological effects have been found in animals exposed to uranium for short- and long-term periods. The primary effects are seen in the kidneys, although developmental/reproductive effects have also been described. Data on kidney effects are available from studies using exposure by gavage, in drinking water, by inhalation, and by parenteral routes.

In the kidney, dose-dependent adverse biochemical and anatomical effects have been noted. The biochemical studies reveal altered levels of certain substances in the plasma and urine. Most of the data on uranium distribution within the kidney indicate that uranium accumulates on the brush border of the epithelial cells lining the lumen of the proximal convoluted tubules. Damage to these cells can result in the observed increase of glucose, low-molecular weight proteins and amino acids in the plasma and urine, indicating that these substances were not properly absorbed by the renal tubules.

The anatomical evidence of lesions in the renal proximal convoluted tubules include cellular necrosis and cellular debris, increased vacuolization, and a loss of brush border microvilli. Some studies show that the renal tubules can repair themselves following insult, but even so, the cells still have a flattened shape and reduced microvilli. In the renal glomerulus, alterations of the podocytes and of the endothelial fenestra were seen, indicating that filtration at this location may also be affected.

Animal studies show that uranium and its compounds can have adverse effects on development and reproduction functions. These studies were often complicated by the induction of maternal toxicity as evidenced by reduced body weights in the treated animals. In mice, uranyl acetate induced embryolethality at a high dose of 25 mg/kg/day and induced reduced fetal body weights at 5 and 10 mg/kg/day (Paternain et al. 1989). Gavage doses of uranyl acetate induced dose-related decreases in fetal weight and increased incidences of skeletal malformations in mice (Domingo et al. 1989a). Rats that were administered uranyl nitrate hexahydrate had fewer litters than controls (Maynard and Hodge 1949). However, when these rats were shifted to a standard diet, the birth rate increased (Maynard et al. 1953). Uranyl nitrate also induced adverse testicular changes following either chronic oral doses of 2 percent in the diet (Maynard et al. 1953), or single intraperitoneal injections (Jadon and Mathur 1983).

There is substantial evidence of the mutagenic effects of radiation in general. However, uranium alone has not been tested. The evidence for the carcinogenicity of radiation is also well established; however, the evidence for the effects of uranium itself is again limited to one study using the inhalation route, and one using high specific activity isotopes injected intravenously.

VI. HEALTH EFFECTS IN HUMANS

The data on the health effects of ingested uranium in humans are limited. The only case studies are from less than a dozen terminally ill patients given uranium intravenously. There is only one epidemiology study regarding health effects in humans following oral exposure. A few epidemiological studies are available on health effects following inhalation exposure at the workplace. None of these studies provide particularly strong evidence that uranium acts as a kidney toxicant in humans. There is one study showing chromosomal aberrations in humans following inhalation exposure in the workplace, and one very brief study on developmental effects in humans.

A. CLINICAL CASE STUDIES

Luessonhop et al. (1958) injected doses of 0.097 to 0.28 uranyl nitrate mg/kg in five terminally ill patients who were in comas. The patients all died from unrelated causes; the time of survival varied widely from 2 to 566 days post-injection. Increased urinary casts were observed in two patients 1 to 9 days post treatment. Two patients showed a transient rise in serum nonprotein nitrogen. Slight drops in serum sodium and serum chloride were also seen. The low number of subjects, and the complications of the patients being terminally ill from brain tumors, preclude the development of firm conclusions from these data.

Bassett et al. (1948) (as reported in Hursh and Spoor [1973] and Moore [1984]) intravenously injected six terminally ill patients with 6 to 71 µg uranyl nitrate/kg. After 5 days, urinary excretion ranged from 71 to 88 percent of the injected dose. For the most part, urinary catalase and urinary proteins were normal. Terepka et al. (1964 as reported in Hursh and Spoor [1973]) injected three normal control subjects with 30 µg uranium^{+6}/kg. Five-day urinary excretion ranged from 68.1 to 71.4 percent.

B. EPIDEMIOLOGICAL STUDIES

The health status was evaluated for persons from two towns in Russia with drinking water that contained 0.04 mg and 0.003 mg uranium/L.

respectively (Novikov et al. 1968; Novikov 1967, 1972). Hematological and biochemical investigations included the following: hemoglobin; blood counts; blood catalase, aldolase, and prothrombin; several vitamins in blood and urine; urinary 17-keto steroids; and electrophoretic analyses of serum proteins. Barring a relative decrease in serum albumin/globulin ratio in the study population of town A, no differences were observed in the two populations.

There are several reports on health effects of inhalation exposure to uranium dusts. Uranium miners and mill workers have been shown to have increased mortality due to lung tumors (Checkoway et al. 1988, Polednak and Frome 1981) or lymphatic tumors (Archer et al. 1973a,b). However, these workers did not show signs of kidney toxicity, indicating that the effect is site-specific, and is unlikely to occur from oral exposure to uranium.

Kidney function was studied in uranium mill workers and compared the results to cement plant workers (Thun et al. 1985). The uranium workers had higher excretion of beta-2-microglobulin and five amino acids (indicating lower tubular reabsorption). Glomerular function (indicated by serum creatinine and creatinine clearance) was actually better in the uranium workers than in the controls.

Waxweiler et al. (1983) investigated a cohort of 2,002 uranium mill workers. The men did not work in the uranium mines and were therefore presumably not exposed to excessive levels of radon gas. Only a small fraction worked more than 5 years. The overall morbidity and mortality due to site specific malignancies was lower than expected. Deaths due to lung cancer were also lower than expected. Significant excess risks for mortality were found for nonmalignant respiratory disease, such as emphysema and fibrosis (SMR = 250). Nonsignificant excesses were found for lymphatic malignancies (SMR=133) and death due to chronic nephritis (SMR = 167) among short-term workers.

Cultured peripheral blood lymphocytes were analyzed from 20 male controls and 80 underground uranium miners from the Colorado Plateau for the prevalence of structural chromosomal aberrations (Brandom et al. 1978). The frequency data were compared between controls and five groups of miners with exposures expressed in working level months (WLM). The WLM for the five groups were as follows: Group I = <100 WLM; Group II = 100 to 470 WLM; Group III = 770 to 1,725 WLM; Group IV = 1,740 to 2,890 WLM; and Group V = >3,000 WLM. The proportion of lymphocytes with any chromosomal aberrations, as well as the proportion with two-hit aberrations, was higher in the miners with a more atypical bronchial cell cytology than in those with normal or mild to moderate atypical cells. In both cases, the difference in chromosomal aberration frequencies was significant ($p < 0.02$), although the radiation exposure was comparable for the two groups. The authors stated that a marked increase in the prevalence of chromosomal aberrations is probably a valid indicator of health risk for miner groups, but that this has only a limited applicability for individual miners. In addition, it should be noted that the radiation risk is mainly from exposure to radon and radon progeny rather than from uranium. Brandom (1981) has also reported that chromosome aberrations and T-cell rosette inhibition tests can be used as sensitive indicators of genotoxic effects.

Wiese (1981) reviewed anecdotal reports of congenital malformations in areas near uranium mines. Interviews of 26 families of miners revealed a slight decrease in sex ratios, but the results were inconclusive.

C. HIGH RISK POPULATIONS

People who are at higher risk for developing toxicity to uranium are in two categories: those who may absorb and accumulate a higher than normal dose, and those with existing disease which may be exacerbated. Persons who may absorb more uranium than normal include those whose food intake is less than average, including those who skip breakfast, and those who are malnourished in general. Persons who are iron-deficient or anemic may also have increased absorption. Since one of the target organs for uranium toxicity is the kidney, persons with existing renal disease may be at greater risk. Fetuses and young children, whose bones are growing, may also accumulate uranium in the skeleton at a higher rate than adults. Animal studies have shown that uranium is toxic to the developing fetus; humans may similarly be at risk.

D. SUMMARY

The human data regarding adverse health effects following ingestion of uranium are minimal. The one existing study shows no adverse effects in the hematological or renal system (Novikov et al. 1968). Data from two injection studies of terminally ill patients (Luessonhop et al. 1958, Bassett et al. 1948) and from one inhalation study of uranium mill workers (Thun et al. 1985) indicate that the kidney may be a target organ, as was seen in animal studies. However, most other inhalation studies on uranium miners and millers do not show adverse kidney effects (Archer et al. 1973, Checkoway et al. 1988, Polednak and Frome 1986, Waxweiler et al. 1983). Uranium workers have shown increases in lung cancer and lymphomas, these are considered to be site-specific effects of radiation. There are anecdotal reports of birth defects in humans related to uranium exposure (Wiese 1981), but these remain to be validated. Chromosomal aberrations in lymphocytes were reported in one study of miners exposed to uranium and other radionuclides in the air (Brandom et al. 1978).

VII. MECHANISM OF TOXICITY

A. IONIZING ENERGY DEPOSITION

The potential for ionizing radiation to cause tissue damage and cancer was established 15 years after the discovery of x-rays (EPA 1989, Upton 1975). Extensive studies have been done on radiation effects in humans and animals following exposure to x-rays, radium, radon, thorium, gamma rays, and other forms of radiation.

Ionizing radiation is not an organ- or tissue-specific carcinogen. Storer (1975) stated: "Ionizing radiation in sufficiently high dosage acts as a complete carcinogen in that it serves as both initiator and promoter. Further, cancers can be induced in nearly any tissue or organ of humans or laboratory animals by the proper choice of radiation dose and exposure schedule." The following tissues have been reported to show radiation-induction of cancers in one or more epidemiological studies in humans: thyroid, female breast, lung, bone marrow (leukemia, multiple myeloma), stomach, liver, large intestine, brain, salivary glands, bone, esophagus, small intestine, urinary bladder, pancreas, rectum, lymphatic tissues, skin, pharynx, uterus, ovary, mucosa of cranial sinuses, and kidney (EPA 1989).

The damage caused by ionizing radiation involves a number of rapid radiochemical reactions. Absorption of energy from alpha and beta particles induces ions and excited radicals in matter, including aqueous solutions. Absorption of energy from x- and gamma radiations by atoms produces electrons ejected from the atoms. These ejected high speed electrons then produce ionizations in the same manner as the alpha and beta particles. These types of interactions occur in about the first 10^{-14} seconds (Bacq and Alexander 1961, Andrews 1961).

The ions and excited radicals induced in cells (aqueous solutions) occur both in organic molecules of the cell contents and in the water surrounding them. In addition, specific compounds, such as H_2O_2, and radicals, such as $HO_2^{\bullet}$, are formed in the water phase. Further chemical interactions can lead to bond scission, chain scission, cross-linking, development of adducts, single and double strand breaks, etc in DNA and in nearby organic molecules. Thus, ionizing radiation can damage proteins, sugars, lipids, enzymes and more importantly, DNA and RNA. These interactions are generally complete by about 10^{-4} seconds after initial exposure (Bacq and Alexander 1961, Andrews 1961).

Ionizing radiation delivered at sufficiently high dose and dose rate leads to cellular death and eventually death of a living organism. At lower doses and dose rates ionizing radiations induce cancer. The ionizing radiations can inhibit mitosis and cause chromosome aberrations including nondisjunction, clastogenesis and point mutations (Andrews 1961, Bacq and Alexander 1961). These effects may be demonstrable minutes to years after exposure.

While carcinogenesis and mutagenesis have not been investigated for every radionuclide, the results of studies that have been performed are consistent with expected effects of ionizing radiation. Mammalian cells in culture have been transformed; chromosomal aberrations have been observed in cultured peripheral lymphocytes; even activation, by frame shift due to a single base deletion in an oncogene, has been reported (EPA 1989). Induction of enzymes of unscheduled DNA repair, perhaps signaling error-prone repair, has also been noted (Tuschl et al. 1980, 1983; Olivieri et al. 1984).

Continuing epidemiological studies have shown increased cancer mortality in persons exposed to x-rays, gamma rays and various internal emitters, such as radon, radium, thorium, at various ages (including in utero) (EPA 1989). Additional support comes from the studies of mice, rats, hamsters, guinea pigs, cats, dogs, sheep, cattle, pigs and monkeys that have demonstrated increased incidence of cancer following exposure to a source of ionizing radiation (EPA 1989).

B. RADIONUCLIDE DOSIMETRY

Since ionizing radiation is known to induce cancer in many organs and tissues, risk estimates for internally deposited radionuclides can be calculated from the distribution of the radionuclides in tissues and the ionizing radiation dose associated with that distribution. The toxicokinetic (metabolic) models used to estimate distribution have been listed in Section IV.D. As explained there, the radionuclide concentration in various organs is calculated for a lifetime intake of 1 pCi per year. For all organs or tissues where there is no organ-specific model, the activity in the organ compartment "other" is considered to be uniformly distributed in all body tissues not specified.

The absorbed radiation dose rate is calculated as follows:

$$\dot{D}_i(X;t) = \sum_{k=1}^{M} D_i(X-Y_k;t)$$

where

$\dot{D}_i(X;t)$ = Absorbed dose rate to organ X at time t due to radionuclide i in source organs Y_1, $Y_2 \ldots . Y_M$.

$D_i(x-Y_k;t)$ = $S_i\ (X-Y_k)\ A_{ik}(t)$

and

$A_{ik}(t)$ = The activity at time t of radionuclide i in source organ Y_k

$S_i(X-Y_k)$ = The S factor

$S_i(X-Y_k)$ = $c \sum_m f_m E_m \phi_m(X-Y_k)$

c = A constant that depends on units of dose, energy and time being used

and there is a summation across all events m of:

f_m = Intensity of decay event (number per disintegration)

E_m = Average energy of decay event in Mev

$\phi_m(X-Y_k)$ = Specific absorbed fraction, i.e., the fraction of emitted energy from source organ Y_k absorbed by target organ X per of X

The S factor is similar to the SEE factor used by the ICRP in ICRP Publication 30. Both S factor and SEE are dosimetric factors to account for the fraction of energy absorbed in a target organ from emission of radiation from a source in another organ, for example, irradiation of a kidney by a radionuclide deposited in bone. However, the SEE factor includes a quality factor for the type of radiation emitted during the transformation (disintegration) (EPA 1989, Dunning et al. 1984).

Summation across all organs and tissues is used to estimate the absorbed dose rate in target organs due to one unit of activity of radionuclide i distributed in source organs $Y_1,\ldots.Y_k$.

The expression for this dose rate is:

$$\dot{D}(X;t) = \sum_k \sum_m A_{ik}(t)\ S_{im}(X-Y_k).$$

Alpha and beta particles are not usually energetic enough to produce significant cross-irradiation terms, so $\phi_m(X-Y) = 0$. The absorbed fraction for alpha and beta particles $[\phi_m\ (X-X)]$ is assumed to be the inverse of the mass of organ X (EPA 1989). Absorbed fractions for beta particles in skeletal tissues are taken from ICRP Publication 30 (ICRP 1980). In the case of alpha particles, special calculations for active bone marrow and endosteal cells in bone are based on the method of Thorne (1977).

A simplified model of the dose rate estimate would be (EPA 1989):

$$\dot{D}_i(t) = \frac{cIf_1\ (f_2')E\ [1-e^{-\lambda_E t}]}{m\dot{\lambda}_E}$$

where:

$\dot{D}(t)$ = organ absorbed dose rate (rad/day)

c = proportionality constant ($[51.2 \times 10^{-6}$ g rad] Ci^{-1} Mev^{-1} d^{-1})

I = radionuclide intake rate (Ci/day)

f_1 = fraction of ingested activity transferred to the blood

f_2' = fraction of blood activity transferred to the target organ

E = energy absorbed by the target organ for each radioactive transformation

m = target organ mass (grams)

λ_E = elimination constant (day^{-1}) $\ln 2/T_E$ or $0.693/T_E$

and

$$T_E = \frac{T_R T_B}{T_R - T_B}$$

where:

T_B = biological removal half-time

T_R = radiological decay half-time

Such a simplified estimate does not include cross-irradiation terms from radionuclides deposited in other nearby organs. These cross-irradiation terms are included in the detailed calculation of radiation dose (S factors) performed by the RADRISK program employed by EPA for calculating radiation dose.

There are some differences between the EPA model and the ICRP models as noted earlier. The EPA calculations carry forward high-LET and low-LET dose rates as separate entities, whereas the ICRP combines high- and low-LET dose rate through the use of a quality factor for high-LET. The ICRP calculations treat radioactive progeny in the body as following the metabolic behavior of the parent nuclide, whereas the EPA model assumes each of the progeny has the metabolic behavior of the elements specific to the progeny. The assumption can have significant impact on the dose estimate (Dunning et al. 1984).

EPA elected to assign the metabolic behavior of progeny on the basis of the elemental form of the progeny. This is clearly appropriate for soft tissues where the elemental form of the progeny will govern their metabolic behavior in the aqueous phase in tissues. In skeletal tissues, however, the progeny may be born and trapped in the crystal lattice of the hydroxyapatite. They would, in this situation, continue to have the metabolic characteristics more like the parent radionuclide (Neuman and Neuman 1958, McLean and Budy 1964). That portion of the progeny born in skeletal tissues outside the crystal lattice would be expected to behave as their elemental characteristics direct them. When radium transforms to radon-222 within a crystal, 70 percent of the radon-222 escapes from the crystal (McLean and Budy 1964); very little of other radon isotopes born in the bone crystal can escape before decaying radiologically.

In estimating radiation risk, EPA usually uses the risk coefficients derived from exposure to low-LET radiation for all tissues except bone, liver and inhaled radon and radon daughters. Bone and liver risk coefficients are derived from high-LET, radium and Thorotrast studies (NAS 1980). Radon and radon daughter risk coefficients are derived from studies of underground miners (NAS 1988). The dosimetry for external x-rays and gamma rays is well established and has minimal uncertainty due to the nature of the radiation. The risk coefficients times the calculated radiation absorbed dose delivered by internally deposited radionuclides, yield the risk. The radiation absorbed dose for internally deposited radionuclides, as noted above, is based on pharmacokinetic models and radiation dosimetric calculations.

The pharmacokinetic models assume uniform distribution of radionuclides in organ or tissues. While many studies have shown uneven distribution of radionuclides in tissues, there are not sufficient data on any radionuclide to establish a detailed pharmacokinetic model using non-uniform tissue or organ nuclide distribution. To the extent that the pharmacokinetic model cannot describe the microscopic distribution of deposited radionuclide within organs, the dose calculated and the risk estimated will be imprecise.

Epidemiologic studies of ingested or injected radionuclides usually involve activity concentrations far in excess of expected environmental exposures. A prime example of this situation can be found in epidemiological studies of persons exposed to radium-226 and radium-228 as dial painters or those injected with radium-226.

The pharmacokinetic model estimated for radium, but taken from studies of persons injected with radium, differs appreciably from the model estimate based on environmental exposure to radium (Stehney and Lucas 1956). In addition, peritrabecular fibrosis has been noted in many species, including humans, following elevated doses of radiation to bone (Sharpe 1976, Lloyd and Henning 1983, Ackerman and Spjut 1962, Sikov and Mahlum 1976, Wilson et al.

1976, Jee et al. 1969, Taylor and Bensted 1969, Clarke 1962). This peritrabecular fibrosis may occur within about 150 days post-exposure, following an abortive attempt by osteoblasts to lay down bone (Jee et al. 1969). At the same time, the microvasculature of bone and bone marrow are disrupted. Jee (1971) reported a 50 percent destruction of marrow vasculature within days of injection of 10 µCi radium-226/kg (Jee 1971). The extensive pathology reported by Jee (1971) following radiation exposure of bone assures that metabolism and physiological responses in bone are abnormal.

The circumstances influencing pharmacokinetics, physiology and pathology must be carefully evaluated for epidemiological studies of internally deposited radionuclides. In particular, it is questionable whether bone with abnormal physiology and metabolism is suitable for estimating pharmacokinetics and whether epidemiology of persons with such internal pathology can be compared to environmental situations. The results of epidemiological studies where pathological conditions are prevalent must be regarded with extreme caution. Risks at environmental exposure levels may, in some cases, be better estimated using risk coefficients derived from penetrating radiation (x- or gamma rays) and pharmacokinetics models than by applying data from epidemiological studies of persons exposed to extremely high activity concentrations of radionuclides.

For many radionuclides there is no direct evidence for carcinogenesis in humans. Often there is little evidence in animal studies. Nevertheless, it must be presumed that such internally deposited radionuclides can cause cancer since they deposit ionization energy in tissues which is no different in character than that which has been shown to be carcinogenic. In such cases, there is little choice but to base risk estimates on dosimetry models and risk coefficients derived from other types of exposures to ionizing radiation.

There is often confusion, however, where populations have been exposed to a radionuclide and followed epidemiologically and found to have no excess cancers in some organs known to be radiosensitive or no excess cancers at all. It is sometimes claimed that in such cases risk estimates should be inferred only for those tissues where the epidemiology shows an excess. This position is not defensible to the Agency. The sensitivity of the epidemiological study must be considered. Unless the exposure level, population size, and period of follow-up are large enough it will be impossible to demonstrate a excess risk from an epidemiological study. (The presence of confounders, including tissue damage, as discussed above, can further obscure a positive correlation between exposure and risk.) Elementary statistical considerations imply that it will be more difficult to demonstrate a statistically significant excess of common cancers; e.g., a larger number of excess cancers is generally required to detect a risk of lung cancer than of bone cancer. Thus, while only excess bone cancers and head carcinomas have been detected in the radium dial painters, this does not automatically imply that all, or even most of the risk from ingested environmental sources of radium is associated with those cancers.

Risk estimates for internally deposited radionuclides should be based on positive epidemiological studies where those are available, but care must be taken in extrapolating to low doses; in particular, tissue damage associated with high dose levels may distort the results. Where direct epidemiological data are lacking, risk estimates can be calculated using the dosimetric methods. Where epidemiological studies exist but show no statistical excess, a careful analysis should be conducted which considers the sensitivity and possible shortcomings of the epidemiologic studies as well as uncertainties in the dosimetric approach. However, even in the absence of direct epidemiological data, use of dosimetry models and risk coefficients is based broadly on the fact that ionizing radiation is a known carcinogen.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

This introductory section summarizes the general approach used to evaluate the hazard of contaminants in drinking water. This text appears in all criteria documents to provide information relevant to the basic issue of how toxicological effects are quantified for chemical toxicity assessment.

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals which do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

A. NONCARCINOGENIC EFFECTS

Method for Quantification of Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), (formerly called the Acceptable Daily Intake (ADI)), is calculated. The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious health effects, even if exposure occurs over a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s). The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{Uncertainty Factor(s)}} = \underline{\qquad} \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Water (OW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS 1977, 1980) as follows:

- An uncertainty factor of 10 is generally used when good chronic, or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic, or subchronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic, or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic, or subchronic toxicity data are available, or when good chronic, or subchronic toxicity data identify a LOAEL, but not a NOAEL for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/OW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving a RfD, the significance of the adverse health effect and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body Weight in kg})}{\text{Drinking Water Volume in L/day}} = \underline{\qquad} \text{ mg/L}$$

where:

Body weight = assumed to be 70 kg for adult
Drinking water volume = assumed to be 2 liters per day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day and Longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using a similar equation to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (\text{L/day})} = \underline{\qquad} \text{ mg/L}$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30-days duration. A Longer-term HA is derived for both the 10-kg child and a 70-kg adult and assumes an exposure period of approximately 7 years (or 10% of an individual's lifetime). A Longer-term HA is generally derived from a study of subchronic duration (exposure for 10 percent of animal's lifetime).

Quantification of Noncarcinogenic Effects

I. One-day and Ten-day Health Advisory

The studies by Maynard and Hodge (1949) were considered for the derivation of the One- and Ten-day HA (Table VIII-1). Insufficient data are available for judging the most appropriate species for extrapolation to humans. The 30-day study with rabbits (Maynard and Hodge 1949) has been selected to serve as the basis for calculation of the Ten-day HA for a 10-kg child. This study was selected because (1) the LOAEL was the lowest calculated; and (2) rabbits appear to be the most sensitive species (rats and dogs were also used) with respect to the acute toxic effects of uranium. Appropriately soluble salts of uranium (uranyl nitrate) were administered to judge the toxicity of uranium in drinking water, and the exposure period was appropriate for judging the effects of 10-day exposures.

In this study, rabbits (six/group, strain and sex not specified) were fed dietary levels of uranyl nitrate of 0, 0.02, 0.1, or 0.5% for 30 days, equivalent to doses of about 2.8, 14, or 71 mg uranium/kg/day, respectively, based on feed conversion ratios of 0.03 (Lehman 1959). Mortality was observed at the high and mid doses (six of six fed 71 mg uranium/kg/day, three of six fed 14 mg uranium/kg/day). Body weight losses were observed at all doses. The high-dose (71 mg uranium/kg/day) lost weight until death by day 10, and the groups fed 2.8 mg uranium/kg/day lost weight during days 14 through 21. Rabbits fed dietary levels of 2.8 mg uranium/kg/day showed body weight losses during days 4 through 7. After 30 days' exposure, body weights were similar to controls in the groups fed 2.8 mg uranium/kg/day but not at the mid and high doses. Renal damage was judged to be moderate at the two low and mid doses and moderately severe at the high dose. These changes were consistent with the nephrotoxic effects of uranium in rats and dogs. Based on this study, the lowest dose tested, 2.8 mg uranium/kg/day, was judged to be a LOAEL. This dose is about twofold lower than the LOAEL for dogs and about thirteen-fold lower than the LOAEL for rats (Table VIII-1). Since the study did not determine a NOAEL, an uncertainty factor of 1,000 is adopted here.

Table VIII-1
A Comparison of 30-Day, 1-Year, and 2-Year NOAELs/LOAELs for Uranium Toxicity Used for the Development of the Ten-day and Longer-term HAs

Species compound	NOAEL (mg uranium/kg/day) 30-day	1-yr	2-yr	LOAEL (mg uranium/kg/day) 30-day	1-yr	2-yr
Rat						
UO_2F_2	19	19	19	39	39	39
$UO_2(NO_3)_2$	24	24	24	120	120	120
UF_4	760	760	760	7,600	7,600	7,600
Dog						
UO_2F_2	4	8	NT	8	19	NT
Rabbit						
$UO_2(NO_3)_2$	ND	NT	NT	2.8	NT	NT

NT = Not tested.
ND = Not determined.

SOURCE: Adapted from Maynard and Hodge (1949).

The One-day and Ten-day HA for a 10-kg child are calculated as follows:

$$\frac{(2.8 \text{ mg uranium/kg/day})(10 \text{ kg})}{(1{,}000)(1 \text{ L/day})} = 0.028 \text{ mg uranium/L } (30\ \mu\text{g uranium/L})$$

(rounded off from 0.028 mg uranium/L)

where:

2.8 mg uranium/kg/day = LOAEL, based on moderately severe renal damage following 30 days of dietary administration of uranyl nitrate to rabbits.

10 kg = assumed body weight of a child.

1 L/day = assumed water consumption of a 10-kg child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

2. Longer-term Health Advisory

The studies by Maynard and Hodge (1949) were considered for derivation of the Longer-term HA (Table VIII-1). In these studies, various uranium compounds (soluble uranium compounds were UO_2F_2, $UO_2(NO_3)_2$, or UF_4) were administered in the diet for periods of 30 days, 1 year, or 2 years to rats, rabbits, and/or dogs. Although the 1- and 2-year studies were performed on rats and dogs, the 30-day feeding study was selected as the basis for the Longer-term HA. Results of these studies indicated that the 1- and 2-year studies in rats and dogs were less sensitive with respect to detecting toxic levels of uranium in the diet than were the 30-day studies in rabbits. Similarly, Willis et al. (1987) found that transient effects on the kidney could be observed in rats exposed to 500 ppm uranium in drinking water that could not be detected in rats exposed to 500, 1,000, or 2,000 ppm after 2 years. Although the chronic toxicity of uranium following oral administration has not been studied in rabbits, inhalation studies conducted by Stokinger et al. (1949) indicate that rabbits exposed to uranium dust (0.25 mg/m^3) for 10 days exhibit similar nephrotoxic effects (mild interstitial nephritis, tubular regeneration) compared with rabbits exposed to these levels for 6.5 months.

The Longer-term HA for a 10-kg child is calculated as follows:

Longer-term HA =

$$\frac{(2.8\ \text{mg uranium/kg/day})\ (10\ \text{kg})}{(1{,}000)(1\ \text{L/day})} = 0.028\ \text{mg/L}\ (30\ \mu\text{g uranium/L})$$

(rounded off from 0.028 mg uranium/L)

where:

2.8 mg uranium/kg/day = LOAEL, based on moderately severe renal damage following 30 days of dietary administration of uranyl nitrate to rabbits.

10 kg = assumed body weight of a child.

1 L/day = assumed water consumption of a 10-kg child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

The Longer-term HA for a 70-kg adult is calculated as follows:

Longer-term HA =

$$\frac{(2.8 \text{ mg uranium/kg/day})(70 \text{ kg})}{(1{,}000)(2 \text{ L/day})} = 0.1 \text{ mg/L } (100\ \mu\text{g uranium/L})$$

(rounded off from 0.098 mg/L)

where:

2.8 mg uranium/kg/day = LOAEL, based on moderately severe renal damage following 30 days of dietary administration of uranyl nitrate to rabbits.

70 kg = assumed body weight of an adult.

2 L/day = assumed water consumption of an adult.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

3. Reference Dose and Drinking Water Equivalent Level

Based on the rationale presented in Section VIII.B, the 30-day rabbit study of Maynard and Hodge (1949) has been selected as the basis for calculation of the Reference Dose (RfD) and Drinking Water Equivalent Level (DWEL). A LOAEL of 2.8 mg uranium/kg/day has been established, based on renal damage in rabbits administered uranium in the diet for up to 30 days.

The DWEL for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{2.8 \text{ mg uranium/kg/day}}{1{,}000} = 0.003 \text{ mg uranium/kg/day } (3\ \mu\text{g uranium/kg/day})$$

(rounded off from 0.0028 mg/kg/day)

where:

2.8 mg uranium/kg/day = LOAEL, based on moderately severe renal damage following 30 days of dietary administration of uranyl nitrate to rabbits.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.003 \text{ mg uranium/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.1 \text{ mg/L } (100\ \mu\text{g uranium/L})$$

where:

0.003 mg uranium/kg/day = RfD.

70 kg = assumed body weight of an adult.

2L/day = assumed daily water consumption of an adult.

B. CARCINOGENIC EFFECTS

Method for Quantification of Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

- Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.

- Group D: Not classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water.

Quantification of Cancer Risk for Chemicals

For chemicals, the data used in these estimates usually come from lifetime exposure studies in animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk for chemicals is usually derived from a linearized multistage model with a 95 percent upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in chemically-caused cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based upon differing assumptions, the estimates which were derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels for chemicals has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

For radionuclides, human epidemiologic data rather than animal experiments form the basis of the cancer risk rate levels, which are derived as best estimates rather than as 95% upper confidence limits of the unit risk from a linearized multistage model. The true risks to humans may be higher or lower than the predicted risks, but the overall uncertainty is probably less than an order of magnitude. Because human data are used, the individual sites of cancer are predicted, as well as the total risk. Therefore, projections can be made both of cancer incidence and of cancer fatality, which are related for a given organ to site-specific survival data, which ranges from 90% survival (10% mortality) for thyroid cancer to 0% survival (100% mortality) for liver cancer (EPA 1989).

Quantification of Carcinogenic Effects

Since the risk calculations in RADRISK are based on annual dose rates, the dose rates at various times during the lifespan are computed for an intake of 1 pCi of a radionuclide per year (Sullivan et al. 1981, Dunning et al. 1980, EPA 1989). The calculated dose rate in a given year for continuous intake is numerically the same as the integrated lifetime dose for the cumulative intake until that year (ICRP 1971). Since a 50 year period is standard for occupational exposure and 70 years is recommended for environmental exposures both calculations are presented here.

As noted earlier, the RADRISK model differs from ICRP models in that no quality factors are used. Instead, separate dose calculation files are maintained for each organ, for high-LET and for low-LET radiations.

RADRISK contains a bookkeeping section of the program that sums intakes, calculates dose rates (see Table VIII-2) and uses the calculated dose rates with risk coefficients (see Table VIII-3) to calculate lifetime risk by organ for high- and low-LET radiations for continuous intake of 1 pCi/year (EPA 1989). An RBE of 8 should be used to estimate risk from high-LET radiation. That is, the risk per low-LET radiation listed in Table VIII-3 should be multiplied by a factor of 8 to obtain a high-LET risk coefficient (EPA 1989).

Irradiation of bone marrow by x-ray or gamma rays or by beta particles leads to leukemia in humans and animals. Leukemia has also been reported in ThO_2 patients and associated with enriched uranium exposure in animals. However, radium dial painters with huge radium deposits in bone have not yielded leukemias as well as bone sarcomas, sinus and mastoid carcinomas. Nor have ankylosing spondylitic patients treated with radium-224 developed an appreciable number of leukemias.

In the case of internally distributed radioisotopes, the dose to "sensitive" tissues is calculated from pharmacokinetic data and physics dosimetry principles. Compared to external x- or gamma exposures which give a fairly uniform dose, internal emitters, particularly alpha emitters, give an irregular, rather uncertain dose distribution. In bone, for example, target cells for osteosarcoma induction are considered to be, and the dose estimated for, cells up to 10 μm from bone surfaces. For leukemia induction, target cells are somewhere in bone marrow. Harley and Pasternack (1976) calculated alpha dose rate for radium-226 and its daughters in uniformly labelled bone in the tissues outside the mineral bone. Noting Lloyd's report (1970) of a 5 μm thick layer of osteoid between mineralized bone surfaces and cellular layers, Harley and Pasternack (1976) adopted a distance of 10 μm from mineral bone as appropriate for calculating endosteal dose. On the other hand, Scott (1967)

Table VIII-2
50-Year Committed Absorbed Dose per Unit Intake (millirad/pCi) from Uranium in Drinking Water

Organ	LLI	Isotope				
		Uranium-238	Uranium-235	Uranium-234	Uranium-233	Uranium-232
Pulmonary Lung	Low	1.06×10^{-7} (1.07×10^{-7})**	2.75×10^{-7} (2.87×10^{-7})**	2.04×10^{-9}	1.83×10^{-9} (1.88×10^{-9})**	3.93×10^{-7} (4.09×10^{-7})**
	High	4.28×10^{-7} (4.28×10^{-7})	4.57×10^{-7} (4.58×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.08×10^{-6}
Stomach	Low	1.08×10^{-7} (1.09×10^{-7})	5.84×10^{-7} (5.91×10^{-7})	6.05×10^{-8}	3.04×10^{-8}	3.16×10^{-7} (3.25×10^{-7})**
	High	6.05×10^{-7} (6.05×10^{-7})	6.42×10^{-7} (6.42×10^{-7})	6.82×10^{-7}	6.90×10^{-7}	1.30×10^{-6}
Intestine	Low	2.35×10^{-6} (2.35×10^{-6})	7.58×10^{-6} (7.59×10^{-6})	6.76×10^{-6}	3.30×10^{-7}	1.06×10^{-6}
	High	2.26×10^{-6} (2.26×10^{-6})	2.37×10^{-6} (2.37×10^{-6})	2.56×10^{-6}	2.59×10^{-6}	3.12×10^{-6}
Kidneys	Low	1.48×10^{-5} (1.48×10^{-5})	4.41×10^{-6} (4.43×10^{-6})	2.50×10^{-7}	1.25×10^{-7}	2.87×10^{-6}
	High	7.32×10^{-6} (7.32×10^{-6})	7.64×10^{-6} (7.64×10^{-6})	8.27×10^{-5}	8.38×10^{-5}	1.95×10^{-4}
Liver	Low	1.12×10^{-7} (1.13×10^{-7})	2.58×10^{-7} (2.67×10^{-7})	1.86×10^{-9}	1.68×10^{-9} (1.71×10^{-9})**	3.21×10^{-8} (3.33×10^{-7})**
	High	3.62×10^{-7} (3.62×10^{-7})	3.79×10^{-7} (3.79×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.10×10^{-6}
Breast	Low	1.09×10^{-7} (1.10×10^{-7})	3.62×10^{-7} (3.75×10^{-7})	2.57×10^{-9}	2.48×10^{-9}	4.37×10^{-7} (4.54×10^{-7})**
	High	4.28×10^{-7} (4.28×10^{-7})	4.57×10^{-7} (4.57×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.08×10^{-6}
Pancreas	Low	1.06×10^{-7} (1.07×10^{-7})	3.72×10^{-7} (3.84×10^{-7})	2.28×10^{-9} (2.31×10^{-9})**	2.18×10^{-9} (2.23×10^{-9})**	4.12×10^{-7} (4.27×10^{-7})**
	High	4.28×10^{-7} (4.28×10^{-7})	4.57×10^{-7} (4.58×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.08×10^{-6}
Red Marrow	Low	5.59×10^{-5} (5.90×10^{-5})	1.58×10^{-6} (1.67×10^{-6})	9.27×10^{-7} (9.76×10^{-7})**	1.58×10^{-7} (1.67×10^{-7})**	4.99×10^{-6} (5.19×10^{-6})**
	High	1.08×10^{-5} (1.14×10^{-5})	1.19×10^{-6} (1.25×10^{-6})	1.28×10^{-5} (1.35×10^{-5})**	1.30×10^{-5} (1.36×10^{-5})	3.85×10^{-5} (4.00×10^{-5})**
Endosteum	Low	1.06×10^{-4} (1.12×10^{-4})	1.77×10^{-4} (1.86×10^{-4})	1.09×10^{-5} (1.15×10^{-5})**	3.94×10^{-7} (4.15×10^{-7})**	1.27×10^{-5} (1.32×10^{-5})**
	High	1.71×10^{-4} (1.80×10^{-4})	1.88×10^{-4} (1.98×10^{-4})	2.03×10^{-4} (2.13×10^{-4})**	2.05×10^{-4} (2.16×10^{-4})	6.13×10^{-4} (6.37×10^{-4})**
Thyroid	Low	9.63×10^{-8} (9.73×10^{-8})	2.36×10^{-7} (2.47×10^{-7})	1.75×10^{-9}	1.50×10^{-9} (1.54×10^{-9})**	2.26×10^{-7} (2.34×10^{-7})**
	High	4.28×10^{-7} (4.28×10^{-7})	4.57×10^{-7} (4.58×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.08×10^{-6}
All other tissue	Low	1.06×10^{-7} (1.07×10^{-7})	3.72×10^{-7} (3.84×10^{-7})	2.28×10^{-9} (2.31×10^{-9})**	2.18×10^{-9} (2.23×10^{-9})**	4.12×10^{-7} (4.27×10^{-7})**
	High	4.28×10^{-7} (4.28×10^{-7})	4.57×10^{-7} (4.58×10^{-7})	4.81×10^{-7}	4.87×10^{-7}	1.08×10^{-6}

**Committed observed dose in the 70th year for continuous intake, otherwise doses in the 50th year and 70th year are the same.

Table VIII-3
Organ-Specific Lifetime Cancer Risks Used in the RADRISK Model from High-LET and Low-LET Irradiation

Organ	LET	Risk/Rad Fatality	Risk/Rad Incidence
Pulmonary Lung	Low	7.0×10^{-5}	7.5×10^{-5}
	High	5.7×10^{-4}	6.0×10^{-4}
Stomach wall	Low	4.6×10^{-5}	6.0×10^{-5}
	High	3.7×10^{-4}	4.8×10^{-4}
Intestine	Low	2.3×10^{-5}	4.3×10^{-5}
	High	1.8×10^{-4}	3.4×10^{-4}
Kidneys	Low	1.8×10^{-5}	4.3×10^{-5}
	High	1.4×10^{-4}	3.4×10^{-4}
Liver	Low	5.0×10^{-5}	5.0×10^{-5}
	High	4.0×10^{-4}	4.0×10^{-4}
Breast	Low	5.5×10^{-5}	1.4×10^{-4}
	High	4.4×10^{-4}	1.1×10^{-3}
Pancreas	Low	3.5×10^{-5}	3.8×10^{-5}
	High	2.8×10^{-4}	3.1×10^{-4}
Red Marrow	Low	4.5×10^{-5}	4.5×10^{-5}
	High	3.6×10^{-4}	3.6×10^{-4}
Bone surface	Low	2.5×10^{-5}	2.5×10^{-6}
	High	2.0×10^{-5}	2.0×10^{-5}
Thyroid	Low	6.4×10^{-5}	6.4×10^{-5}
	High	5.1×10^{-5}	5.1×10^{-4}
Esophagus	Low	9.1×10^{-6}	9.1×10^{-6}
	High	7.3×10^{-5}	7.3×10^{-5}
Lymphoma	Low	1.4×10^{-5}	1.9×10^{-5}
	High	1.1×10^{-4}	1.5×10^{-4}
All other tissue	Low	1.9×10^{-5}	3.4×10^{-5}
	High	1.6×10^{-5}	2.7×10^{-4}

Adapted from Tables 6-6 and 6-7 in EPA (1989).

indicated cell nuclei at a distance of 10 to 15 µm from mineralized bone surface in rats, and James and Taylor (1971) calculated dose out to a distance of 20 µm from bone surface. The International Commission on Radiological Protection (ICRP) (1968) recommended calculating endosteal dose rate over a distance 5 to 10 µm from the trabecular surface.

Mays and Tueller (1964) calculated doses for radium-226 out to 70 µm from bone surface and stated that the average dose rate for soft tissues from 0 to 10 µm was used because: (a) osteosarcoma induction appeared to occur in cells adjoining bone surfaces and (b) dose-rates were maximum at bone surfaces. They also reported Owen's (1963) suggestion that cells located over 1 cell-layer from bone surfaces were at risk. Vaugan (1972) had shown a 5 to 20 µm thick cell layer in rabbits and Lloyd and Henning (1983) demonstrated a single cell layer 0.6 to ≥8.1 µm thick in human bone.

Bone is the archetypical example of the problems with alpha emitting isotopes. The short range of the alpha particle in tissue and the high rate of deposition of energy make the distance from source to target cells a very important consideration. The situation described for bone is true, to a greater or lesser extent for all tissues with a non-uniform distribution of radioisotope. This complicates direct application of a risk coefficient derived from gamma exposure with a dose calculation using a pharmacokinetic model. It also increases the uncertainty in the risk assessment.

Several of the questions posed by the SAB Radiation Advisory Committee led to adjustment of the draft risk estimates. Review of both risk coefficients and dosimetric calculations revealed places where EPA assumptions could be improved based on current data. All calculations except those for gamma and photon emitters were adjusted for bone marrow (Tables VIII-4 and VIII-5) risk estimates if necessary. Adjustments were made as shown in the following sections.

Table VIII-4
Estimated Risk of Death from Leukemia or All Causes from Ingestion of 70.765 pCi Uranium
(f_1 = 0.05)
Red Marrow: High-LET

Isotope	Lifetime Risk (Deaths in Cohort)	Current Risk Coefficient/pCi (Deaths in Cohort)	Risk Coefficient (Deaths/µCi)	Lifetime All Causes Mortality (Deaths/µCi)
U-232	7.443×10^{-5}	1.052×10^{-6}	1.052×10^{-5}	4.839×10^{-5}
U-233	2.517×10^{-5}	3.577×10^{-7}	3.557×10^{-6}	1.903×10^{-5}
U-234	2.493×10^{-5}	3.523×10^{-7}	3.523×10^{-6}	1.946×10^{-5}
U-235	2.307×10^{-5}	3.260×10^{-7}	3.260×10^{-6}	1.926×10^{-5}
U-238	2.076×10^{-5}	2.934×10^{-7}	2.934×10^{-6}	1.922×10^{-5}

The risk of leukemia following exposure to alpha emitters does not seem to be the same as that following gamma exposure. EPA estimates the leukemia fatality risk as 358.1×10^{-6}/person rad using the risk derived from gamma exposure and an RBE of 8 (EPA 1989). The corresponding incidence would be identical. All calculations were adjusted for bone marrow risk estimates (Tables VIII-4 and VIII-5) as suggested by the SAB Radiation Advisory Committee. The leukemia fatality risk calculated for uranium should be reduced by the ratio of (50×10^{-6}/person rad) ÷ ($358{:}1\times10^{6}$/person rad) or 0.1396.

The BEIR IV Committee estimated leukemia risk as 50×10-6 to 60×10-6/person rad based on thorotrast data (NAS 1980). Mays et al. (1985) estimated the leukemia risk as 40×10-6/person rad, also based on thorotrast data. For this document a leukemia risk estimate of 50×10-6/person rad will be used.

Table VIII-5
Adjusted Risk of Death from Leukemia from Ingestion of 70.765 pCi Uranium
(f_1 = 0.05)
Red Marrow: High-LET

Isotope	Adjusted Marrow Risk (Deaths/µCi)	Decrease in Marrow Risk (Deaths/µCi)	Adjusted Lifetime Risk (Deaths/µCi)
U-232	1.469×10^{-6}	9.051×10^{-6}	3.934×10^{-5}
U-233	4.967×10^{-7}	3.060×10^{-6}	1.657×10^{-5}
U-234	4.920×10^{-7}	3.031×10^{-6}	1.643×10^{-5}
U-235	4.553×10^{-7}	2.805×10^{-6}	1.646×10^{-5}
U-238	4.097×10^{-7}	2.524×10^{-6}	1.670×10^{-5}

In the case of radium-224 exposure, leukemia has occurred, but in very small numbers. Mays et al. (1986) reported three excess cases of leukemia in 681 adults with an average skeletal dose of 206 rad, following treatment with radium-224. Wick et al. (1986) reported seven excess bone marrow failures and one excess leukemia in 1,501 adults with an average skeletal dose of 56 rad, following treatment for ankylosing spondylitis with radium-224.

Mays et al. (1986) also pointed out that analgesic drugs often given for spondylitis are suspected of causing leukemias (Mays et al. 1986). Although the cases listed above may not be related to the radium-224 exposure, they can be evaluated to calculate the dose-response estimate if they were radiation-related.

The endosteal dose is about 8.9 times the average skeletal dose for radium-224 (Spiess and Mays 1970, Marshall et al. 1978). The marrow dose is about 0.09 times the endosteal dose (ICRP 1979, EPA 1989). The marrow doses for the cases listed above would be: 1) (206 rad) (8.9)(0.09) = 165 rad and 2) (56 rad)(8.9)(0.09) = 45 rad.

(1) The leukemia dose response for Mays et al. would be:

$$\frac{\text{3 leukemia cases}}{\text{(681 persons) (165 rad/person)}} = 2.7 \times 10^{-5} \text{ leukemia cases/person rad}$$

(2) The leukemia dose response for Wick et al. would be:

$$\frac{\text{1 leukemia case}}{\text{(1501 persons)(45 rad/person)}} = 1.5\text{x}10^{-5} \text{ leukemia cases/person rad}$$

If all bone marrow failures are included:

$$\frac{\text{7 bone marrow failures}}{\text{(1501 persons)(45 rad/person)}} = 104\text{x}10^{-6} \text{ bone marrow failures/person rad}$$

In the Spiess study, there were five blood dyscrasias, one of which was a lymphatic leukemia, in 1970 (Spiess et al. 1970), among 708 adults with an average skeletal dose of 204 rads. The bone marrow failure rate is then:

$$\frac{\text{5 bone marrow failures}}{\text{(708 person)(163 rad/person)}} = 43\text{x}10^{-6} \text{ bone marrow failures/person rad}$$

The calculation of urinary cancers in RADRISK involves multiplying the kidney dose rate times a relative risk coefficient. A single relative risk coefficient was used because the kidney and bladder have about the same relative risk after radiation exposure (Sullivan et al. 1981, NAS 1980). The kidney dose rate was used because it was thought to be more reliable than the bladder estimate. Where there is little difference between kidney and bladder dose rates, there is no problem. Unfortunately, some alpha-emitter dose rates to the kidney can be much greater than the bladder dose rates. To correct for this disparity, the risk to the urinary system can be adjusted as follows:

(1) To correct the mortality estimate:

$$\text{adjusted risk/original risk} = \frac{(1 - C)}{2}$$

where:

C = bladder dose rate/kidney dose rate

(2) To correct the incidence estimate:

$$\text{adjusted risk/original risk} = \frac{(1 - 2C)}{2}.$$

These corrections presume the risk per unit dose for kidney and bladder are proportional to their respective baseline rates and are approximately equal for mortality, while the bladder incidence risk is twice that of the kidney. The adjusted risks are listed in Table VIII-6.

Table VIII-6
Adjusted Urinary Cancer Risks

Isotope	Lifetime Risk/μCi (Deaths/μCi)	Decrease in Risk (Deaths/μCi)	Adjusted Lifetime Mortality (Death/μCi)	Final Mortality (Deaths/μCi)
U-232	2.520×10^{-5}	1.268×10^{5}	3.934×10^{-5}	2.666×10^{-5}
U-233	1.101×10^{-5}	5.538×10^{-6}	1.657×10^{-5}	1.103×10^{-5}
U-234	1.087×10^{-5}	5.468×10^{-6}	1.643×10^{-5}	1.096×10^{-5}
U-235	1.010×10^{-5}	5.080×10^{-6}	1.646×10^{-5}	1.138×10^{-5}
U-238	9.858×10^{-6}	4.959×10^{-6}	1.670×10^{-5}	1.174×10^{-5}

Estimated lifetime risk for ingestion of various uranium isotopes in drinking water are listed in Table VIII-7. Concentrations of these isotopes in drinking water yielding specific risks are listed in Table VIII-8.

Table VIII-7
Estimated Lifetime Risk for Ingestion of 1 µCi of Uranium of Drinking Water (f_1 = 0.05)

Isotope	Current		Revised	
	Incidence (Cases)	Mortality (Deaths)	Incidence (Cases)	Mortality (Deaths)
U-232	8.826×10^{-5}	4.839×10^{-5}	3.723×10^{-5}	2.666×10^{-5}
U-233	3.599×10^{-5}	1.903×10^{-5}	1.613×10^{-5}	1.103×10^{-5}
U-234	3.550×10^{-5}	1.946×10^{-5}	1.600×10^{-5}	1.096×10^{-5}
U-235	3.512×10^{-5}	1.926×10^{-5}	1.640×10^{-5}	1.138×10^{-5}
U-238	3.506×10^{-6}	1.922×10^{-5}	1.627×10^{-5}	1.174×10^{-5}

Table VIII-8
Water Concentration of Uranium in Drinking Water to Yield a Specific Risk for Lifetime Consumption

Isotope	Concentration in pCi/L to Produce					
	4 mrem/yr EDE		10^{-4} Incidence		10^{-4} Mortality	
	Current[a]	Revised[b]	Current[a]	Revised[b]	Current[a]	Revised[b]
U-232	2	8	6	52	10	72
U-233	5	20	14	120	26	174
U-234	5	20	14	121	26	175
U-235	5	21	14	118	26	168
U-236	6	21	15	128	27	185
U-237	1780	1770	2020	2180	3610	3860
U-238	6	22	15	119	26	163
U-240	1540	1420	1740	1660	3030	2890
$\frac{\text{U-234+238}}{2}$	6	21	14	120	26	170

[a] f_1 = 0.20; with no adjustment of osteosarcoma or urinary risk estimates.

[b] f_1 = 0.05.

IX. UNCERTAINTY ANALYSIS

Assessment of the carcinogenicity of the radionuclides of uranium is uncertain in several areas. These areas of uncertainty include: the metabolic model, including absorption, distribution and dosimetry; the risk coefficients used for calculating lifetime risk; and factors influencing both.

A. UNCERTAINTY IN CHOICE OF METABOLIC MODEL

One issue is the proper choice of the gut-to-blood absorption factor (f_1) for uranium. The most widely quoted estimates are in the range of 0.01 to 0.30, although even this range does not completely encompass the data (Wrenn et al. 1985, Schlenker and Oltman 1981, Adams and Spoor 1974). The ICRP model adopted here by EPA assumes an f_1 of 0.05; however, the ICRP publication suggests that at low (environmental) levels of uranium the appropriate f_1 may be higher - about 0.20. On the other hand, measurements of urinary excretion here suggested values as low as about 0.01 for f_1 if all uranium absorbed is excreted in urine.

In assessing the uncertainty relating to f_1 one should keep in mind that it is the dose to target organs (or cells) that we are interested in and not the f_1 per se. The organ doses depend also on rates of uranium uptake from blood (f_2') and of loss from the organ. In principle, one can partly bypass the problem of determining these metabolic parameters and assess the dose to bone or kidney for a given intake by simply measuring skeletal or kidney burden under steady state conditions. However, an important limitation to this approach is the difficulty in estimating past intake.

Spencer et al. (1973) pointed out the reasons for unreliability in data obtained from short-term balance studies. They concluded that only multiple 6-day metabolic study periods with fecal markers given at the beginning and end of each study period provided interpretable information on mineral balances. Spencer et al. (1990) reported results of a multiple 6-day study series on uranium metabolism in four subjects. They concluded that about 5 percent of the uranium in water was absorbed and excreted in urine, urinary excretion was about 2 percent of total excretion, and there was a large uncertainty in the determination.

Ultimately, a uranium metabolic model should explain both body burden data and measurements of short-term uptake and excretion. Unfortunately, the experimental data are conflicting and additional measurements are required to resolve these conflicts before a metabolic model can be developed with confidence.

Estimates of body burden and the distribution of uranium among organs vary widely (Fisenne et al. 1988, Wrenn et al. 1985). One of the problems is in getting representative samples of tissue, particularly of the skeleton. Although some investigators assume no differences in concentrations of uranium between rib, sternum and vertebrae (Fisenne and Welford 1986), others have pointed out the variability in uranium concentrations between and within bones may be one or two orders of magnitude (Singh et al. 1987, Schlenker and Oltman 1981). Singh and Wrenn (1987) concluded, "Thus, any estimate of uranium skeletal burden based on the uranium concentration of an individual bone is likely to be erroneous."

Uncertainty in skeletal burden, in turn, influences estimates of total body burden, metabolic model and dosimetry. For a specific intake, the calculated body burden may be changed by changing the assumed fraction absorbed, the fraction transferred to an organ, or the retention of the radioisotope in various organs. If intake and body burden are specified, then varying any metabolic parameter requires that some other parameter(s) change in compensation to maintain the constant body burden.

Wrenn et al. (1985), reviewed uranium metabolic data and proposed a metabolic model that differs substantially from that used in ICRP; in particular, Wrenn et al. recommended an f_1 value of only 0.014 under environmental conditions. As shown in Table IX-1, however, this model actually projects a higher bone burden (bone dose) than the ICRP model in which f_1 is taken to be 0.05. The estimated kidney burden (dose) is, however, about 3 times lower with Wrenn's model.

Table IX-1
Comparison of Burden Predicted in Bone
and Kidney by ICRP and by Wrenn et al.

Model	f_1	Kidney Burden	Bone Burden
ICRP (1979)	0.05	1.0	1.0
ICRP (1979)*	0.20	4.0	4.0
Wrenn et al. (1985)	0.014	0.31	1.28

*Relative to recommended ICRP model (f_1 = 0.05).

Durbin (1987) reviewed a number of models of uranium metabolism, from an early general equilibrium model, which gave a gastrointestinal absorption factor of 0.15 to 0.30, to a recent biokinetic model developed by Lipsztein, which gave a self-consistent set of parameter values when gastrointestinal absorption was taken to be 0.20. Also of interest is the model of Fisher (1987) which corrects the soft tissue retention function for uranium released from bone and kidney reservoirs. A reexamination of uranium metabolism in light of newly reported data (Fisenne and Welford 1986, Fisenne et al. 1988, Singh et al. 1987) could reduce the uncertainties in estimates of dose and risk.

The uncertainty in organ doses associated with uncertainty in the choice of metabolic model is difficult to estimate, given the lack of consistency in the observations. However, it would appear that the EPA (ICRP) model may underestimate or overestimate doses by a factor of about 4.

B. UNCERTAINTY IN DISTRIBUTION OF ISOTOPE

The alpha emitting radionuclides, of which uranium is a representative, are not well characterized with respect to distribution in the human body. The distribution between and within bones of the skeleton has been reported in some studies (Schlenker and Oltman 1981, Singh et al. 1987); others have determined the distribution between and within soft tissues (Spoor 1968, Donoghue et al. 1972, Struxness et al. 1956, Fisenne and Welford 1986). Uncertainty in distribution within organs will influence dose and risk calculations. The combined uncertainty of tissue distribution and individual variability in distribution among organs may introduce a factor of 2 in uncertainty.

C. UNCERTAINTY IN DOSIMETRIC CALCULATIONS

While calculations of average dose deposited in a tissue may be fairly accurate, this may not accurately reflect the dose to target cells for induction of cancer. This is particularly true for alpha emitting nuclides due to the short range of alpha particles in tissue. The problem can be exemplified in the periosteal dose in bone that might induce osteosarcoma.

Harley and Pasternack (1976) calculated alpha dose rate for radium-226 and its daughters in uniformly labelled bone in the tissues outside the mineral bone. Noting Lloyd's report (1970) of a 5 µm thick layer of osteoid between mineralized bone surfaces and cellular layers, Harley and Pasternack (Harley and Pasternack 1976) adopted a distance of 10 µm from mineral bone as appropriate for calculating endosteal dose. On the other hand, Scott (Scott 1967) estimated cell nuclei to be at a distance of 10 to 15 µm from mineralized bone surface in rats, and James and Taylor (1971) calculated dose out to a distance of 20 µm from bone surface. ICRP (1968) recommended calculating endosteal dose rate over a distance 5 to 10 µm from the trabecular surface.

Mays and Tueller (1964) calculated doses for radium-226 out to 70 µm from bone surface and stated that the average dose rate for soft tissues from 0 to 10 µm was used because osteosarcoma induction appeared to occur in cells adjoining bone surfaces, and dose rates were maximum at bone surfaces. They also cited Owen's suggestion (1968) that cells located over one cell layer away from bone surfaces were at risk. Vaugan (1972) had found a 5 to 20 µm thick cell layer in rabbits, and Lloyd and Henning (1983) demonstrated a single cell layer 0.6 to ≥8.1 µm thick in human bone. Currently, the dose from bone surface to cells up to 10 µm from bone surface is used to estimate osteosarcomigenic dose.

It is difficult to quantitatively assess the uncertainty in risk associated with the uncertainty in dose. This is in part due to confounding with problems of non-homogeneous distribution of the alpha emitting radionuclides. EPA expects that while individual cancers may be uncertain by factors up to 10, the overall risk should be within a factor of roughly 5.

D. UNCERTAINTY IN SPECIFIC ORGAN RISKS

Based on the doses calculated using the ICRP metabolic model, it would appear that the most important potential target organs for carcinogens by ingested uranium are bone, bone marrow, and kidney.

Bone and Bone Marrow

In the case of uranium in bone and bone marrow, we have essentially the same types of uncertainties as we have in evaluating the risks from radium-226 deposited in bone (See Criteria Document for Radium). With respect to bone cancer, for example, the shape of the dose-response relationship may be an issue.

The EPA risk model for alpha emitters deposited in bone projects substantially fewer leukemias than bone cancers. As discussed in the Radium Criteria Document, a much higher leukemia risk estimate would be obtained by multiplying the calculated bone marrow dose by the low-LET leukemia risk factor and by the assumed relative biological effectiveness (RBE) of 8. This approach to calculating leukemia risk due to alpha emitters was rejected in view of epidemiological data on cohorts ingesting or injected with radium-224, radium-226 and thorium-232, all of which indicated that the approach based on extrapolation from low-LET observations greatly overstated the risk. Possible explanations for this discrepancy are discussed more fully in the Radium Criteria Document. Part of the explanation may be related to possible shielding of sensitive marrow cells from alpha particles released from radionuclides deposited in bone; perhaps sensitive cells for leukemogenesis are not located near bone surfaces. However, it is also possible that the high doses occurring in the epidemiological studies resulted in extensive killing of the highly radio-sensitive marrow cells, obscuring the carcinogenic potential of the radiation. Thus, it is conceivable that leukemia may be a more common outcome than bone cancer at the lower alpha particle doses with which we are concerned. If on this premise, the alpha particle leukemia risk estimate was to be based on the low-LET risk estimate, as discussed above, EPA's estimate of leukemia risk from ingested uranium would be increased by about a factor of 7, but the overall cancer risk would be increased by less than 20 percent.

Kidney Risk

Uranium has been found to be concentrated in the kidney. The risk of kidney cancer from a given dose of alpha radiation is highly uncertain. Atomic bomb survivors show an excess of kidney cancer, but the uncertainty bounds are large, extending from no excess attributed to radiation to more than half of all urinary cancers. There is also more direct evidence from patients injected with radium-224 that alpha irradiation can cause kidney cancer (Spiess 1991). For the purposes of this rulemaking, EPA has based its risk estimate on the A-bomb survivor data (NAS 1980), assuming that kidney cancer accounts for half the urinary cancer risk and the RBE for alpha particles is 8. Given the uncertainty over RBE, the actual risk may be a factor of 2 or 3 higher; alternatively, in view of the statistical uncertainties in the A-bomb survivor data, the actual kidney risk may be very low. If the risk of kidney cancer were to be neglected, the EPA risk estimate for uranium would be reduced by 25 percent or less.

E. UNCERTAINTY IN OTHER FACTORS INFLUENCING RISK

There are a number of factors that might influence uranium risk. In particular, there is about a 3-fold uncertainty in the risk coefficients used to calculate the risk per unit intake (EPA 1989).

When considering specific individual rather than population (average) risk, variability in physiological parameters must be considered. These will include such factors as age, genetic makeup, gender, and diet. For example, uranium absorption may be substantially increased after overnight fasting, depending on iron intake (Sullivan et al. 1986b, Sullivan and Ruemmler 1988, LaTouche et al. 1987, Bhattacharyya et al. 1989).

F. CONCLUSION

In conclusion, there are many uncertainties in estimating the risk from ingested uranium that stem from uncertainties in metabolism (internal dosimetry) and in the appropriate risk factors for specific tissues. Overall, EPA regards its risk estimate as a reasonable central estimate but emphasizes that the actual risk could easily be a factor of 5 higher or lower.

X. REFERENCES

Ackerman LV, Spjut HJ. 1962. Tumors of Bone and Cartilage. Armed Forces Institute of Pathology, Washington, DC.

Adams N, Spoor NL. 1974. Kidney and bone retention functions in the human metabolism of uranium. Phys. Med. Bio. 19:460-471.

Adams N, Hunt BW, Reisland TA. 1978. Annual Limits of Intake of Radionuclides for Workers, NRPB-R82. National Radiological Protection Board, Harwell, Didcot.

Allard B, Kipatsi H, Torstenfelt B, et al. 1979. Nuclide transport by groundwater in Swedish bedrock. Mater. Res. Soc. Symp. Proc. 403-410.

Allard B, Olofsson U, Torstenfelt B, et al. 1982. Sorption of actinides in well-defined oxidation states on geologic media. Mater. Res. Soc. Symp. Proc. 11:775-782.

Ames LL, McGarrah JE, Walker BA. 1982. Sorption of uranium and cesium by Hanford basalts and associated secondary smectite. Chem. Geol. 35:205-225.

Andrews HL. 1961. Radiation Biophysics. Prentice-Hall, Edgewood Cliffs, NJ.

Archer, VE, Wagoner JK, Lundin FE. 1973a. Lung cancer among uranium miners in the United States. Health Phys. 25:351-371.

Archer VE, Wagoner JK, Lundin FE Jr. 1973b. Cancer mortality among uranium mill workers. J. Occup. Med. (United States) 15:11-14.

ATSDR. 1990a. Toxicological profile for uranium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR. 1990b. Toxicological profile for plutonium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR. 1990c. CDC Subcommittee Report on Biological Indicators of Organ Damage. Public Health Service. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Avasthi PS, Evan AP, Hay D. 1980. Glomerular endothelial cells in uranyl nitrate-induced acute renal failure in rats. J. Clin. Invest. 65:121-127.

Bacq ZM, Alexander P. 1961. Fundamentals of Radiobiology. 2nd Edition. Pergamon Press, New York.

Bassett SH, Frenkel A, Cedars N, et al. 1948. The excretion of hexavalent uranium following intravenous administration. II. Studies on human subjects. USAEC Report UR-37.

Begovich C, Eckerman K, Schlatter EC, Ohr SY, Chester RO. 1981. DARTAB: A program to combine airborne radionuclide environmental exposure tabulations of predicted health impacts. ORNL-5692. Oak Ridge National Laboratory, Oak Ridge, TN.

Belova RS, Lunkina ZP. 1967. The radium and uranium in foodstuffs and their accumulation in human teeth. Gig. i. Sanit. 32:48-51.

Bentley KW, Stockwell DR, Britt KA, Kerr CB. 1985. Transient proteinuria and aminoaciduria in rodents following uranium intoxication. Bull. Environ. Contam. Toxicol. 34:407-416.

Bernard SR, Snyder WS. 1975. Metabolic Models for Estimation of Internal Radiation Exposure Received by Human Subjects from the Ingestion of Noble Gases. Health Physics Division Progress Report, ending June 20, 1975. ORNL-5046. Oak Ridge National Laboratory, Oak Ridge TN.

Berdnikova AV. 1964. Of the uranium content in the external environment and the human excreta. Vopr. Pitaniya. 23:17-20 [Russian]

Bernard SR, Struxness EG. 1957. A Study of the Distribution and Excretion of Uranium in Man: An Interim Report. Oak Ridge, TN: Oak Ridge National Laboratory. ORNL-2304.

Bhattacharyya M, Larsen R, Cohen N, et al. 1989. Gastrointestinal absorption of plutonium and uranium in fed and fasted adult baboons and mice: Application to humans. Radiat. Prot. Dosimetry 28:159-165.

Bowman FJ, Foulkes EC. 1970. Effects of uranium on rabbit renal tubules. Toxicol. Appl. Pharmacol. 16:391-399.

Brandom WF. 1981. Potential bioassays for the detection of the effects of underground mining. In: Radiation Hazards in Mining. Society of Mining Engineers, NY, pp. 207, 212.

Brandom WF, Saccomano G, Archer VE, Archer PG, Bloom AD. 1978. Chromosome aberrations as a biological dose-response indicator of radiation exposure in uranium miners. Radiat. Res. 76:159-171.

Broadway JH, Strong AB. 1983. Radionuclides in human bone samples. Health Phys. 45:765-768.

Brown, KW. 1983. Hazardous Waste Land Treatment. Boston, MA: Butterworth Publishers.

Brunskill GJ, Wilkinson P. 1987. Annual supply of uranium-228, uranium-234, thorium-230, radium-226, lead-210, polonium-210 and thorium-232 to lake 239 [Experimental Lakes Area, Ontario (Canada)] from terrestrial and atmospheric sources. Can. J. Fish. Aquat. Sci. 44(Suppl 1):215-230.

Butterworth A. 1955. The significance and value of uranium in urine analysis. Trans. Assoc. Ind. Med. Off. 5:36-43.

Checkoway H, Pearce N, Crawford-Brown D, Cragle D. 1988. Radiation dose and cause-specific mortality among workers at a nuclear materials fabrication plant. Am. J. Epidem. 127:255-266.

Clarke WJ. 1962. Comparative histopathology of Pu ^{239}, Ra^{226}, and Sr^{90} in pig bone. Health Phys 8:621-627.

Cooper JR, Stradling GN, Smith H, et al. 1982. The behavior of uranium-233 oxide and uranyl-233 nitrate in rats. Int. J. Radiat, Biol. Relat. Stud. Phys., Chem. Med. 41:421-433.

Cottrell WD, Haywood FF, Witt DA, et al. 1981. Radiological Survey of the Shpack Landfill, Norton MA. Report: ISS DOE/EV-0005/31. DE2004939.

Crawford-Brown D. 1983. An age-dependent model for the kinetics of uptake and removal of radionuclides from the G.I. tract. Health Phys. 44:609.

Dean MH. n.d. Personal communication (1967) as cited in Hursh and Spoor 1973.

de Rey BM, Lanfranchi HE, Cabrini RL. 1984. Deposition pattern and toxicity of subcutaneously implanted uranium dioxide in rats. Health Phys. 46:688-692.

Diamond GL, Morrow PE, Panner BJ, Gelein RM, Baggs RB. 1989. Reversible urbanyl fluoride nephrotoxicity in the Long Evans rat. Fund. and Appl. Toxicol. 13:65-78.

Domingo JL, Llobet JM, Tomas JM, Corbella J. 1987. Acute toxicity of uranium in rats and mice. Bull. Environ. Contam. Toxicol. 39:168-174.

Domingo JL, Paternain JL, Llobet JM, Corbella J. 1989a. The developmental toxicity of uranium in mice. Toxicology 55:143-152.

Domingo JL, Ortega A, Paternain JL, Corbella J. 1989b. Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. Arch. Environ. Health. 44:395.

Donoghue JK, Dyson ED, Hislop JS, Leach AM, Spoor NL. 1972. Human exposure to natural uranium. Br. J. Ind. Med. 29:81-89.

Dounce AL. 1949. The mechanism of action of uranium compounds in the animal body. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill, pp. 951-991.

Dunning DE, Leggett RW, Yalcintas MG. 1980. A Combined Methodology for Estimating Dose Rates and Health Effects from Exposures to Radioactive Pollutants. ORNL/TM-7105. Oak Ridge National Laboratory, Oak Ridge, TN.

Dunning DE, Leggett RW, Sullivan RE. 1984. An assessment of health risk from radiation exposures. Health Phys 46:1035-1051.

Durbin PW. 1984. Metabolic models for uranium. In: Moore RH, ed. Biokinetics and Analysis of Uranium in Man. Proceedings of a colloquium held at Richland, WA. August 8-9, 1984. Prepared by the Hanford Environmental Health Foundation for the Department of Energy. Available from NTIS, U.S. Department of Commerce, Springfield, VA.

Durbin PW. 1987. Metabolic models for uranium. In: Biokinetics and Analysis of Uranium in Man. USUR-05 HEHF-47. Hanford Environmental Health Foundation, Richlands, Washington. pp. F-1 to F-65.

Durbin PW, Wrenn ME. 1975. Metabolism and effects of uranium in animals. In: Proceedings of the Conference on Occupational Health Experience with Uranium, U.S. Energy Research and Development Administration, ERDA 93/UC 41. pp. 65-129.

Dygert HP, LaBelle CW, Laskin S, et al. 1949. Toxicity following inhalation. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill. pp. 423-700.

Environmental Protection Agency (EPA). 1985. Nationwide occurrence of radon and other natural radioactivity in public water supplies. Montgomery, AL: Office of Radiation Programs. EPA 520/5-85-008.

Environmental Protection Agency (EPA). 1985. Radionuclides: Background information document-standard for radon-222 emissions from underground uranium mines. Report. U.S. Environmental Protection Agency, Office of Radiation Standards, Washington, DC. EPA 520/1-85-010. NTIS PB86-244936/GAR.

Environmental Protection Agency (EPA). 1986. Final rule for radon-222 emissions from licensed uranium mill tailings. Background information document. Report. EPA 520/1-86-009. NTIS PB87-207569.

Environmental Protection Agency (EPA). 1989. Risk Assessments Methodology. Environmental Impact Statement, NESHAPS for Radionuclides. Background Information Document - Volume 1 EPA/520/1-89-005. EPA, Washington, DC.

Environmental Protection Agency (EPA). 1991. Health Effects Assessment Summary Tables (HEAST). OERR 9200.6-303(91-1). Office of Radiation Protection, Washington, DC.

Finkel MP. 1953. Relative biological effectiveness of radium and other alpha emitters in CF No. 1 female mice. Proc. Soc. Exp. Biol. Med. 83:494-498.

Fisenne IM, Perry PM. 1985. Isotopic U concentration in human blood from New York City donors. Health Phys. 49:1272-1275.

Fisenne IM, Welford GA. 1986. Natural uranium concentrations in soft tissues and bone of New York City residents. Health Phys. 50:739-746.

Fisenne IM, Perry PM, Harley NH. 1988. Uranium in humans. Rad. Prot. Dosim. 24:127-131.

Fish BR, Payne JA, Thompson JL. 1960. Ingestion of uranium compounds. In: Oak Ridge National Laboratory, Health Physics Division, Annual Report, Oak Ridge National Laboratory, Oak Ridge, TN. ORNL-2994. pp. 269-272.

Fisher DR. 1987. Internal Dosimetry of Uranium. In: Biokinetics and Analysis of Uranium in Man. USUR-05 HEHF-47. Hanford Environmental Health Foundation, Richland, Washington. pp. G-1 to G-24.

Fisher DR, Jackson PO, Brodaczynski GG, Scherpelz RI. 1983. Levels of 234U, 238U and 230th in excreta of uranium mill crushermen. Health Phys. 45:617-629.

FRDS. 1986. Federal Reporting Data System. Facilities and population served by primary water supply sources (FRDS 07). FY85. April 9, 1986.

Garten CT. 1978. A review of parameter values used to assess the transport of Pu, U and Th in terrestrial food chains. Environ. Res. 17:437-452.

Gindler JE. 1973. Physical and chemical properties of uranium. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium, Plutonium, Transplutonic Elements: Handbook of Experimental Pharmacology XXXVI. New York: Springer-Verlag. pp. 69-164.

Goel KA, Garg VK, Garg V. 1979. Histopathological alterations induced by uranyl nitrate in the liver of albino rat. Bull. Environ. Contam. Toxicol. 22:785-790.

Goel KA, Garg VK, Garg V. 1980. Histopathology of kidney of albino rat poisoned with uranyl nitrate. Bull. Environ. Contam. Toxicol. 24:9-12.

Haley DP. 1982. Morphologic changes in uranyl nitrate induced acute renal failure in saline- and water-drinking rats. Lab. Invest. 46:196-208.

Hamilton JG. 1948. The metabolic properties of the fission products and actinide elements. Rev. Mod. Phys. 20:718-728.

Hamilton EI. 1972. The concentration of uranium in man and his diet. Health Phys. 22:149-153.

Harley NW, Pasternack BS. 1976. A comparison of the dose to cells on trabecular bone surfaces from plutonium-239 and radium-226 Based on experimental alpha absorption measurements. Health Phys. 30:35-46.

Harrison JD, Stather JW. 1981. The gastrointestinal absorption of proactinium, uranium, and neptunium in the hamster. Rad. Res. 88:47-55.

Hart DR, McKee PM, Burt AJ, Goffin MJ. 1986. Benthic community and sentiment quality assessment of Port Hope Harbour, Lake Ontario. J. Great Lakes Res. 12:206-220.

Haven FL, Hodge HC. 1949. Toxicity following the parenteral administration of certain soluble uranium compounds. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill. pp. 281-308.

Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co. pp. 1071-1072.

Herczeg AL, Simpson HJ, Anderson RF, et al. 1988. Uranium and radium mobility in groundwaters and brines within the Delaware basin, southeastern New Mexico, U.S.A. Chem. Geol. 72:181-196.

Hess CT, Michel J, Horton TR, et al. 1985. The occurrence of radioactivity in public water supplies in the United States. Health Phys. 48:553-586.

HSDB. 1991. Uranium. Hazardous Substances Data Base.

Hursh JB, Spoor NL. 1973. Data on man. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium, Plutonium, Transplutonic Elements: Handbook of Experimental Pharmacology XXXVI. New York: Springer-Verlag. pp. 197-239.

Hursh JB, Neuman WF, Toribara T, et al. 1969. Oral ingestion of uranium by man. Health Phys. 17:619-621.

International Commission on Radiological Protection (ICRP). 1968. A Review of the Radiosensitivity of the Tissues in Bone, ICRP Publication 11. Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1971. The Assessment of Internal Contamination Resulting from Recurrnet or Prolonged Uptakes. ICRP Publication 10A, Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1973. Alkaline Earth Metabolism in Adult Man, ICRP Publication 20. Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1975. Report of the Task Group on Reference Man. ICRP Publication 23. Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1979. Limits for Intakes of Radionuclides by Workers, ICRP Publication 30, Part 1. Annals of the ICRP, Vol 3 (3/4). Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1980. Limits for Intakes of Radionuclides by Workers. ICRP Publication 30, Part 2. Annals of the ICRP 4(3/4), Pergamon Press, New York.

International Commission on Radiological Protection (ICRP). 1981. Limits for Intakes of Radionuclides by Workers, ICRP Publication 30, Part 3. Annals of the ICRP, Vol 6 (2/3). Pergamon Press, New York.

ILO. 1983. International Labour Office. Encyclopedia of Occupational Health and Safety, 3rd ed. Geneva, Switzerland.

Jadon A, Mathur R. 1983. Gametogenic count and histopathological effect of thorium nitrate and uranyl nitrate on mice testes. Andrologica 15:40-43.

James AC, Taylor DM. 1971. DTPA therapy for chelation of 239Pu in bone: the influence of bone remodelling. Health Phys. 21:31-39.

Jee WSS. 1971. Bone-seeking radionuclides and bones. In: Pathology of Irradiation. CC Berdjis, ed. Williams & Wilkins Co., Baltimore. pp 186-212

Jee WSS, Bartley MH, Dockum NL, et al. 1969. Vascular changes in bones following bone-seeking radionuclides. In: Delayed Effects of Bone-Seeking Radionuclides. CW Mays et al., eds. University of Utah Press, Salt Lake City. pp. 437-455.

Kathren RL. 1984. Radioactivity in the Environment. London: Harwood Academic.

Katz JJ, Rabinowitch E. 1951. The Chemistry of Uranium the Element, Its Binary and Related Compounds. New York: Dover Publications.

Kobayashi S, Nagase M, Honda N, et al. 1984. Glomerular alterations in uranyl acetate-induced acute renal failure in rabbits. Kidney Int. 26:808-815.

Kuroda PK, Essien IO, Sandoval DN. 1984. Fallout of uranium isotopes from the 1980 exception of Mount St. Helens. J. Radionucl. Chem. 84:23-32.

Larsen RP, Bhattacharrya MH, Oldham RD, et al. 1984. Gastrointestinal absorption and retention of plutonium and uranium in the baboon. In: Argonne National Laboratory, Environmental Research Division, Annual Report, July 1982-June 1983, Argonne National Laboratory, Argonne, IL. ANL-83-100. pp. 51-60.

LaTouche YD, Willis DL, Dawydiak OI. 1987. Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. Health Phys. 53:147-162.

Leach LJ, Maynard EA, Hodge CH, et al. 1970. A five-year inhalation study with natural uranium dioxide dust - I. Retention and biologic effect in the monkey, dog and rat. Health Phys. 18:599-612.

Leach LJ, Yuile CL, Hodge HC, et al. 1973. A five-year inhalation study with natural uranium dioxide (UO_2) dust. II. Post-exposure retention and biological effects in the monkey, dog, and rat. Health Phys. 25:239-258.

Leggett RW. 1989. The behavior and chemical toxicity of uranium in the kidney: A reassessment. Health Phys. 57:365-383.

Lide DR. 1990. CRC handbook of chemistry and physics. Boston: CRC Press, pp. 4-35-4-40, 4-114-4-115.

Lloyd E. 1970. Argonne National Laboratory Report ANL 7760. Part 2. (As cited in Harley and Pasternak 1976).

Lloyd EL, Henning CB. 1983. Cells at risk for the production of bone tumors in radium exposed individuals: An electron microscope study. Health Phys 44(Supp 1):135-148.

Longtin JP. 1987. Radon, radium, and uranium occurrence in drinking water from groundwater sources. Presented at the 1987 American Water Works

Association Conference, Kansas City, Missouri, June 14, 1987. Office of Drinking Water, Technical Support Division, U.S. Environmental Protection Agency, Cincinnati, OH.

Longtin JP. 1988. Occurrence of radion, radium, and uranium in groundwater. J Am Water Works Assn, pp. 84-93.

Longtin J. 1990. Occurrence of radionuclides in drinking water, a national study. In: Radon, Radium and Uranium in Drinking Water, Cothern CR and Rebers PA, Eds., Lewis Publishers, pp. 97-140.

Luessenhop AJ, Gallimore JC, Sweet WH, Struxness EG, Robinson J. 1958. The toxicity in man of hexavalent uranium following intravenous administration. Am. J. Roentgenol. 79:83-100.

Marshall JH, Groer PG, Schlenker RA. 1978. Dose to endosteal cells and relative distribution factors for radium-224 and plutonium-239 compared to radium-226. Health Phys. 35:91-101.

Masuda K. 1971a. Intake and urinary excretion of uranium in non-occupationally exposed persons: I. Recovery of uranium in the daily diet and urine. Japn. J. Hyg. 26:434-437.

Masuda K. 1971b. Intake and urinary excretion of uranium in non-occupationally exposed persons: II. Uranium in the daily diet. Japn. J. Hyg. 26:438-441.

Masuda K. 1971c. Intake and urinary excretion of uranium in non-occupationally exposed persons: III. Urinary excretion of uranium. Japn. J. Hyg. 26:442-446.

Masuda K. 1971d. Intake and urinary excretion of uranium in non-occupationally exposed persons: IV. Discussions on dietary intake and urinary excretion of uranium. Japn. J. Hyg. 26:447-450.

Maynard EA, Hodge HC. 1949. Study of toxicity of various uranium compounds when fed to experiment animals. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill, pp. 309-376.

Maynard EA, Downs WL, Hodge HC. 1953. Oral toxicity of uranium compounds. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill, pp. 1221-1369.

Mays CW. 1988. Alpha-particle-induced cancer in humans. Health Phys. 55:637-652.

Mays CW, Tueller AB. 1964. Determination of localized alpha-dose IV in soft tissue near radioactive bone. In: Research in Radiobiology. University of Utah Report COO-229. pp. 199-205.

Mays CW, Rowland RE, Stehney AF. 1985. Cancer risk from the lifetime intake of Ra and U isotopes. Health Phys. 48:635-647.

Mays CW, Spiess H, Chemelevsky D, et al. 1986. Bone sarcoma cummulative tumor rates in patients ingested with ^{224}Ra. In : The Radiobiology of Radium and Thorotrast. Gossner W, Gerber GB, Hazen U, et al., eds. Urban and Schwarzenberg, Baltimore. pp. 27-31.

McLean FC, Budy AM. 1964. Radiation, Isotopes, and Bone. Academic Press, New York.

Meglen RR. 1985. Dietary intake computations for radionuclides. Prepared from monitoring data provided by Science Applications International Corporation. Prepared by Robert R. Meglen, Center for Environmental Sciences, University of Colorado at Denver. December, 1985.

Moore RH, ed. 1984. Biokinetics and Analysis of Uranium in Man. Proceedings of a colloquium held at Richland, WA. August 8-9, 1984. Prepared by the Hanford Environmental Health Foundation for the Department of Energy. Available from NTIS, U.S. Department of Commerce, Springfield, VA.

Morrow P, Gelein R, Beiter H, Scott J, Picano J, Yuile C. 1982. Inhalation and intravenous studies of UF_6/UO_2F_2 in dogs. Health Phys. 43:859.

National Academy of Sciences (NAS). 1977. Drinking Water and Health. Safe Drinking Water Committee. National Academy of Sciences, Washington, DC.

National Academy of Sciences (NAS). 1980. The effects on populations of exposures to low levels of ionizing radiation. Report of the Committee on the Biological Effects of Ionizing Radiation (BEIR III Report), Washington, DC.

National Academy of Sciences (NAS). 1983. National Academy of Sciences. Drinking Water and Health. Vol. 5. Washington, DC: National Academy Press.

National Academy of Sciences (NAS). 1988. Health Risks of Radon and other Internally Deposited Alpha-Emitters. Report of the Committee on the Biological Effects of Ionizing Radiations (BEIR IV). National Academy of Sciences, Washington, DC.

National Council on Radiation Protection and Measurements (NCRP). 1984. Radiological assessment: Predicting the transport, bioaccumulation and uptake by man of radionuclides released to the environment. NCRP Report No. 76. Bethesda, MD: NCRP.

National Council on Radiation Protection and Measurements (NCRP). 1984. Exposures from the uranium series with emphasis on radon and its daughter. NCRP Report No. 77. Bethesda, MD: NCRP.

National Council on Radiation Protection and Measurements (NCRP). 1987. Exposure of the population in the United States and Canada from Natural Background Radiation. Report No. 94, Bethesda, MD, December 30, 1987, pp. 1-209.

National Council on Radiation Protection and Measurements (NCRP). 1987. Exposure from the uranium series with emphasis on radon and its daughters. NCRP Report No. 77, Bethesda, MD. Issued January 15, 1987. 132 pp.

Neuman WF, Neuman MW. 1958. The Chemical Dynamics of Bone Mineral. Chicago: University of Chicago Press.

Novikov YV. 1972. Hygienic standardization of the permissible amount of uranium in drinking water. Gig. Sanit. 37:13-17.

Novikov YV. 1967. The effect of low concentration of uranium in drinking water on the health of the population. Hyg. Sanit. (translation of Gig. Sanit.) 33:340-344.

Novikov YV, Rezanov II. 1962. On the uranium content of drinking water of ground orgin and its excretion in urine and feces. Gig. I. Sanit. 27:103-105 [Russian]

Novikov YV, Pushkina NN, Tambovtseva AM. 1968. The effects on man of low concentrations of uranium. Hyg. Sanit. (translation of Gig. Sanit.) 33:340-344.

Nozaki T, Ichikowa M, Sasuga T, Inarida M. 1970. Neutron activation analysis of uranium in human bone, drinking water and daily diet. J. Radioanalyt. Chem. 6:33-40.

Oak Ridge National Laboratories (ORNL). 1981. Uranium in U.S. surface, ground, and domestic waters. EPA Report No. EPA-570/9/81/001.

Olivieri G, Bodycote J, Wolff S. 1984. Adaptive Response of Human Lymphocytes to Low Concentrations of Radioactive Thymidine. Science 223:594-597.

Ortega A, Domingo JL, Lloket JM, et al. 1989. Evaluation of the oral toxicity of uranium in a 4-week drinking water study in rats. Bull. Environ. Contam. Toxicol. 42:935-941.

Owen M. 1963. Cell population kinetics of an osteogenic tissue: I and II. Brookhaven National Laboratory Reports BNL-6737 (1963) and BNL-6738 (1963). As cited in Mays and Tueller 1964.

Paternain JL, Domingo JL, Ortega A, et al. 1989. The effects of uranium on reproduction, gestation, and postnatal survival in mice. Ecotox. Environ. Saf. 17:291-296.

Pelayo JC, Andrews PM, Coffey AK, Calcagno PL, Eisner GM, Jose PA. 1983. The influence of age on acute renal toxicity of uranyl nitrate in the dog. Pediat. Res. 17:985-992.

Polednak AP, Frome EL. 1986. Mortality among men employed between 1943 and 1947 at a uranium processing plant. J. Occup. Med 23:169-178.

Premuzic ET, Francis AJ, Lin M, Schubert J. 1985. Induced formation of chelating agents by Pseudomonas aeruginosa grown in presence of thorium and uranium. Arch. Environ. Cont. Toxicol. 14:759-768.

Reid DG, Sackett WM, Spaulding RF. 1977. Uranium and Radium in Livestock Feed Supplements. Health Phys. 32:535-540.

Roswell RL, Wrenn ME. 1980. Model for uranium metabolism in man. In: Annual Report, Radiobiology Laboratory, University of Utah, Salt Lake City, UT.

SAIC. 1985. Estimated national occurrence and exposure to uranium in public drinking water supplies. Prepared by Science Applications International Corporation.

SAIC. 1987. Estimated national occurrence and exposure to uranium in public drinking water supplies. Prepared by Science Applications International Corporation. October 22, 1987.

Sax NI, Lewis RJ. 1987. Hawley's Condensed Chemical Dictionary. 11th ed. Van Nostrand Reinhold: New York.

Schlenker RA, Oltman BG. 1981. Uranium concentrations in human bone. In: Wrenn M, ed. Actinides in Man and Animals. R.D. Press, Salt Lake City. pp. 473-482.

Scott BL. 1967. J. Cell Biol. 35:115. As cited in Harley and Pasternack 1976)

Sharpe WD. 1976. Chronic radium intoxication: Morphology of bone and marrow infarcts. In : The Health Effects of Plutonium and Radium. WSS Jee, ed. The J.W. Press, Salt Lake City. pp 457-483.

Sheppard MI, Vandergraaf TT, Thibault DH, et al. 1983. Technetium and uranium: Sorption by and plant uptake from peat and sand. Health Phys. 44:635-644.

Sikov MR, Mahlum DD. 1976. Influence of age and physiochemical form on the effects of ^{239}Pu on the skeleton of the rat. In: The Health Effects of Plutonium and Radium. WSS Jee, ed. The J.W. Press, Salt Lake City. pp 33-47.

Singh NP, Wrenn ME. 1987. Uptake of uranium from drinking water. In: Hemphill DD, ed. Trace substances in environmental health. Columbia, MO: University of Missouri, pp. 203-212.

Singh NP, Bennett DB, Wrenn ME. 1987. Macro-distribution of naturally occurring α-emitting isotopes of uranium in the human skeleton. Health Phys. 52:769-773.

Singh NP, Burleigh DP, Ruth HM, Wrenn ME. 1990. Daily uranium intake in Utah residents from food and drinking water. Health Phys. 59(3):333-337.

Somayajulu BLK, Meghani CA, Borole DV. 1980. Uranium in drinking waters: rejection by human body. In: Patel B, ed. Management of the Environment. New Delhi: Wiley Eastern, pp. 528-532.

Sorg T. 1990. Removal of uranium from drinking water by conventional treatment methods. In: Radon, Radium and Uranium in Drinking Water, Cothern CR and Rebers PA, Eds., Lewis Publishers, pp. 173-192.

Spencer H, Freedland JA, Ferguson V. 1973. Human balance studies in mineral metabolism. In: Zipkin, I, ed. Biological Mineralization. John Wiley & Sons, New York. pp. 689-727.

Spencer H, Osis D, Fisenne I, Perry P, Harley N. 1990. Measured intake and excretion patterns of naturally occurring 234U, 238U and calcium in humans. Radiat. Res. 124:90-95.

Spiess H. 1991. Later effects in 224Radium treated juvenile and adults patient. In: Radiation Protection Programme Progress Report 1986-89. Vol. 2. EEC, EURATOM, Brussels. pp. 1576-1585.

Spiess H, Mays CW. 1970. Bone cancers induced by 224Ra (Thx) in children and adults. Health Phys. 19:713-729.

Spiers FW, Lucas HF, Rundo J, et al. 1983. Leukaemia incidence in the U.S. dial workers. Health Phys. 44(Suppl 1):65-72.

Spoor NW. 1968. Occupational Hygiene Standards for Natural Uranium. AHSB(RP)R77. Authority Health and Safety Branch, UKAEA, Harwell.

Stehney AF, Lucas HF Jr. 1956. Studies on the radium content of humans arising from the natural radium of their environment. In: Proceeding of the International Conference on the Peaceful Uses of Atomic Energy, Geneva, 1955. Volume II, Biological Effects of Radiation. United Nations, New York. pp. 49-54.

Stelling JHE. 1980. Source Category Survey: Uranium Refining Industry. Report. EPA-450/3-8-010. NTIS PB80-192867.

Stevens WF, Bruenger W, Atherton DR, et al. 1980. The distribution and retention of hexavalent ^{233}U in the beagle. Radiat. Res. 83:109-126.

Stokinger HE. 1981. Uranium, U. In: Clayton GD, Clayton FE, eds. Industrial hygiene and toxicology, Vol. 2A. 3rd ed. New York, NY: John Wiley & Sons, pp. 1995-2013.

Stokinger HE, Baxter RC, Dygert HP, LaBelle CW, et al. 1949. Toxicity following inhalation for 1 and 2 years. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGray Hill. pp. 1370-1378.

Stone RS, Bencosme SA, Latta H, Madden SC. 1961. Renal tubular fine structure studies during reaction to acute uranium injury. Arch Pathol 71:160.

Storer JB. 1975. Radiation Carcinogenesis. In: Cancer 1, F.F. Becker, ed. Plenum Press, New York. pp. 453-483.

Stroube WB, Jelinek CF, Baratta EJ. 1985. Survey of radionuclides in foods, 1978-1982. Health Phys. 49:731-736.

Struxness EG, Luessenhop AJ, Bernard SR, Gallimore JC. 1956. The distribution and excretion of hexivalent uranium in man. In: Peaceful Uses of Atomic Energy. Proceedings of the International Conference. Volume 10, Radioactive Isotopes and Nuclear Radiations in Medicine. United Nations, New York. pp. 186-196.

Sullivan MF. 1980. Absorption of actinide elements from the gastrointestinal tract of rats, guinea pigs, and dogs. Health Phys. 38:159-171.

Sullivan MF, Ruemmler PS. 1988. Absorption of ^{233}U, ^{237}Np, ^{238}Pu, ^{241}Am and ^{244}Cm from the gastrointestinal tracts of rats fed an iron-deficient diet. Health Phys. 54:311-316.

Sullivan MF, Miller BM, Ryan JL, et al. 1983. Gut-related studies of radionuclide toxicity. In: Pacific Northwest Laboratory Annual Report for 1983. Richland, WA: Pacific Northwest Laboratory. PNL-4600, Pt. 1. pp. 95-99.

Sullivan MF, Ruemmler P, Buschbom R. 1986a. Influence of iron on plutonium absorption by adult and neonatal rat. Toxicol. Appl. Pharmacol. 85:239.

Sullivan MF, Ruemmler PS, Ryan JL, Bushhom RL. 1986b. Influence of oxidizing on reducing agents on gastrointestinal absorption of U, Pu, Am, Cm and Pm by rats. Health Phys. 50:223-232.

Sullivan RE, et al. 1981. Estimates of Health Risk from Exposures to Radioactive Pollutants, ORNL/TM-7745. Oak Ridge National Laboratory, Oak Ridge, TN.

Swanson SM. 1985. Food chain transfer of U-Series radionuclides in northern Saskatchewan aquatic system. Health Phys. 49:747-770.

Tannenbaum A, Silverstone H. 1951. Some aspects of the toxicology of uranium compounds. In: Tannenbaum A, ed. Toxicology of uranium compounds. New York, NY: McGraw-Hill, pp. 59-96.

Taylor DM, Bensted JPM. 1969. Long-term biological damage from plutonium-239 and americium-241 in rats. In: Delayed Effects of Bone-Seeking Radionuclides. CW Mays et al., eds. University of Utah Press, Salt Lake City. pp 357-370.

Thompson DL. 1976. Uranium in dental porcelain. Report. NTIS PB-259624.

Thorne MD. 1977. Aspects of the dosimetry of alpha-emitting radionuclides in bone with particular emphasis on ^{226}Ra and ^{239}Pu. Phys Med Biol 22:36-46.

Thorne MC. 1988. Commentary on the discussion. Intern. J. Rad. Biol. 53:530-539.

Thun MJ, Baker DB, Steenland K, et al. 1985. Renal toxicity in uranium mill workers. Scand. J. Work Environ. Health 11:83-90.

Tracy BL, Quinn JM, Gilman AP, et al. 1983. The metabolism of ingested uranium in mammals. In: Broerse, JJ, et al., eds. Proceedings of the 7th International Congress of Radiation Research. Amsterdam: Martinus Nijhoff. Paper E5-18.

Terepka AR, Toribara TY, Newman WE. 1864. Skeletal retention of uranium in man. Presented at 46th Meeting of Endocrinology Society. San Francisco, June 18, 1964. As Cited by Hursh and Spoor 1973.

Tuschl H, Altmann H, Kovac R, et al. 1980. Radiation on Repair Processes on Human Lymphocytes. Radiat Res 81:1-9.

Tuschl H, Kovac R, Altmann H. 1983. UDS and SCE in lymphocytes of persons occupationally exposed to low levels of ionizing radiation. Health Phys. 45:1-7.

Upton AC. 1975. Physical Carcinogenesis: Radiation - History and Sources. In: Cancer 1, F.F. Becker, ed. Plenum Press, New York. pp. 387-403.

USDI. 1980. US Department of the Interior. Depleted uranium. Washington, DC, Bureau of Mines Bulletin 671.

Van Netten C, Morley DR. 1983. Uptake of uranium molybdenum copper and selenium by the radish from uranium rich soils. Arch. Env. Health. 38:172-175.

Vaugan J. 1972. Bone surfaces: What are they? In: Radiobiology of Plutonium. Stover BJ, Jee WSS, eds. J.W. Press, Salt Lake City. pp. 323-332.

Voegtlin C, Hodge HC, eds. 1949. Pharmacology and toxicology of uranium compounds. Vols. 1 and 2. New York: McGraw-Hill.

Voegtlin C, Hodge HC, eds. 1953. Pharmacology and toxicology of uranium compounds. Vols. 3 and 4. New York, NY: McGraw-Hill.

Wade Miller Associates, Inc. (WMA). 1990. Occurrence and exposure assessment for uranium in public drinking water supplies. Prepared for USEPA Office of Drinking Water under EPA Contract 68-03-3514, April 26.

Waxweiler RJ, Archer VE, Roscoe RJ, et al. 1983. Mortality patterns among a retrospective cohort of uranium mill workers. Presented at Epidemiology Applied to Health Physics. Proceedings of Health Physics Society, pp. 428-435.

Weast R, ed. 1985. CRC Handbook of Chemistry and Physics. 66th ed. Boca Raton, FL: CRC Press, pp. B146; B440-441.

Weast RC. 1986. CRC Handbook of Chemistry and Physics. 67th ed. Boca Raton, FL: CRC Press, Inc. pp. B141-142.

Weigel F. 1983. Uranium and uranium compounds. In: Grayson M, ed. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 23, 3rd ed. New York: John Wiley and Sons, pp. 502-547.

Welford GA, Baird R. 1967. Uranium levels in human diet and biological materials. Health Phys. 13:1321.

Welford GA, Baird R, Fisenne IM. 1970. Preliminary results: Uranium in man. The 16th Annual Bioassay and Analytical Conf., Bethesda, MD. October 8-9.

Wick RR, Chemelevsky D, Gossner W. 1986. ^{224}Ra risk to bone and haematoporetic tissue in ankylosing spondylitis patients. In : The Radiobiology of Radium and Thorotrast. Gossner W, Gerber GB, Hagen U, et al., eds. Urban and Schwarzenberg, Baltimore. pp. 38-44.

Wiese WH. 1981. Birth effects in areas of uranium mining. In: Radiation Hazards in Mining. Society of Mining Engineers, NY. pp. 605-607.

Willis DL, LaTouche D, Dawydiak OJ. 1987. Chronic studies of uranium toxicity in rats from drinking water. Res. Notes 171.

Wilson FD, Pool RR, Stitzel K, et al. 1976. The bone-bone marrow interface (Endosteum) potential relationship of microenvironments in the regulation of response to internal emitters. In: The Health Effects of Plutonium and Radium. WSS Jee, ed. The J.W. Press, Salt Lake City. pp. 617-642.

Wrenn ME, Durbin PW, Howard B, et al. 1985. Metabolism of ingested U and Ra. Health Phys. 48:601-633.

Wrenn ME, Liese G, Torrey J, et al. 1986. The elimination rate of uranium from the kidney of the dog. In: Research in Radiobiology. Annual Report of Work in Progress in the Internal Irradiation Program. Department of Pharmocology, University of Utah School of Medicine.

Wrenn ME, Singh NP, Ruth H, Burleigh D. 1988. Gastrointestinal Absorption of Soluble Uranium from Drinking Water. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA/600-D88/078.

Wrenn ME, Singh NP, Ruth H, Burleigh D. 1989. Gastrointestinal absorption of soluble uranium from drinking water by man. Radiat. Protect. Dosimetry 26:119-122.

Yang IC, Edwards KW. 1984. Releases of radium and uranium into Ralston Creek and Reservoir Colorado USA from uranium mining. In: Barney GS, Navratil JD, Schulz W, eds. 185th meeting: American Chemical Society Symposium Series 246. Geochemical behavior of disposed radioactive waste, Seattle WA, March 20-25, 1983. Washington, DC: American Chemical Society, pp. 271-286

Yuile CL. 1973. Animal experiments. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium, Plutonium, Transplutonic Elements: Handbook of Experimental Pharmacology XXXVI. New York: Springer-Verlag. pp. 165-196.